Barbara O'Brien


```
=> fil reg; d ide
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DICTIONARY FILE UPDATES:  22 FEB 2007  HIGHEST RN 922800-14-4

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TSCA INFORMATION NOW CURRENT THROUGH June 30, 2006

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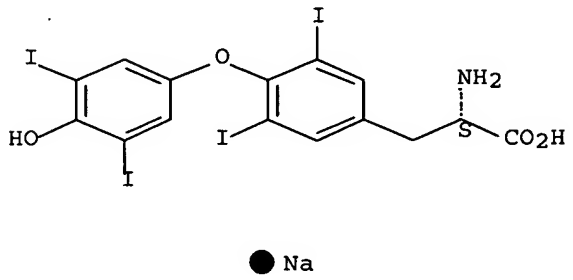
http://www.cas.org/ONLINE/UG/regprops.html


L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2007 ACS on STN
RN   55-03-8  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   L-Tyrosine, O-(4-hydroxy-3,5-diiodophenyl)-3,5-diiodo-, monosodium salt
     (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Thyroxine, monosodium salt, L- (8CI)
OTHER NAMES:
CN   Berlthyrox
CN   Dathroid
CN   Droxine
CN   Eferox
CN   Elthyrone
CN   Elthyroxine
CN   Eltroxin
CN   Euthyrox
CN   Eutirox
CN   L-Thyroxin Henning
CN   L-Thyroxine monosodium salt
CN   L-Thyroxine sodium
CN   L-Thyroxine sodium salt
CN   Laevoxin
CN   Letrox
CN   Letter
CN   Levaxin
CN   Levo-T
CN   Levoroxine
CN   Levothroid
CN   Levothyrox
CN   Levothyroxine sodium
CN   Levotirox
```

CN Levotiroxina
CN Levoxyl
CN Monosodium thyroxine
CN NSC 259940
CN Oroxine
CN Puran T 4
CN Sodium L-thyroxine
CN Sodium levothyroxine
CN Sodium thyroxin
CN Sodium thyroxinate
CN Sodium thyroxine
CN Synthroid
CN Synthroid sodium
CN Synthrox
CN T 4KP
CN Thevier
CN Throxinique
CN Thyradin
CN Thyradin S
CN Thyrax Duotab
CN Thyrex
CN Thyro 4
CN Thyrosit
CN Thyroxevan
CN Thyroxine sodium
CN Thyroxine sodium salt
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
FS STEREOSEARCH
DR 50809-32-0, 67809-22-7
MF C15 H11 I4 N O4 . Na
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSCOSEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, PIRA, PROMT, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
CRN (51-48-9)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

488 REFERENCES IN FILE CA (1907 TO DATE)
488 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

INVENTOR SEARCH

=> fil capl; d que 17; fil medl; d que 118; fil embase; d que 135; fil drugu; d que 138; fil wpix; d que 152; fil ipa; d que 165
FILE 'CAPLUS' ENTERED AT 12:39:53 ON 23 FEB 2007
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FILE COVERS 1907 - 23 Feb 2007 VOL 146 ISS 10
FILE LAST UPDATED: 22 Feb 2007 (20070222/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

L2	13	SEA FILE=CAPLUS ABB=ON	SCHREDER S?/AU
L3	2	SEA FILE=CAPLUS ABB=ON	NISCHWITZ M?/AU
L5	1	SEA FILE=REGISTRY ABB=ON	"LEVOTHYROXINE SODIUM"/CN
L6	488	SEA FILE=CAPLUS ABB=ON	L5
L7	2	SEA FILE=CAPLUS ABB=ON	(L2 OR L3) AND L6

FILE 'MEDLINE' ENTERED AT 12:39:53 ON 23 FEB 2007

FILE LAST UPDATED: 22 Feb 2007 (20070222/UP). FILE COVERS 1950 TO DATE.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

L16	3	SEA FILE=MEDLINE ABB=ON	SCHREDER S?/AU
L17	0	SEA FILE=MEDLINE ABB=ON	NISCHWITZ M?/AU
L18	3	SEA FILE=MEDLINE ABB=ON	(L16 OR L17)

FILE 'EMBASE' ENTERED AT 12:39:53 ON 23 FEB 2007

FILE COVERS 1974 TO 23 Feb 2007 (20070223/ED)

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L24             7 SEA FILE=EMBASE ABB=ON  SCHREDER S?/AU
L25             0 SEA FILE=EMBASE ABB=ON  NISCHWITZ M?/AU
L35             7 SEA FILE=EMBASE ABB=ON  (L24 OR L25)
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```
FILE 'DRUGU' ENTERED AT 12:39:53 ON 23 FEB 2007
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FILE LAST UPDATED: 23 FEB 2007        <20070223/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<
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L36             3 SEA FILE=DRUGU ABB=ON  SCHREDER S?/AU
L37             0 SEA FILE=DRUGU ABB=ON  NISCHWITZ M?/AU
L38             3 SEA FILE=DRUGU ABB=ON  (L36 OR L37)
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FILE 'WPIX' ENTERED AT 12:39:54 ON 23 FEB 2007
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FILE LAST UPDATED:                    19 FEB 2007   <20070219/UP>
MOST RECENT THOMSON SCIENTIFIC UPDATE:    200712    <200712/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> YOU ARE IN THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX <<<

>>> IPC Reform reclassification data for the backfile is being
    loaded into the database during January 2007.
    There will not be any update date (UP) written for the reclassified
    documents, but they can be identified by 20060101/UPIC. <<<

FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf
```

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>>> FOR DETAILS ON THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX
    PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

>>> New and revised Manual Codes went live in Derwent World Patents Index
    To view the lists of new, revised and retired codes for both CPI and
    EPI,  please go to:
    http://scientific.thomson.com/dwpi-manualcoderevision <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE


L43            7 SEA FILE=WPIX ABB=ON  SCHREDER S?/AU
L44            2 SEA FILE=WPIX ABB=ON  NISCHWITZ M?/AU
L45           72 SEA FILE=WPIX ABB=ON  (LEVOTHYROXINE/BI,ABEX OR (LEVO/BI,ABEX
                 OR L/BI,ABEX)(W)THYROXINE/BI,ABEX)(1A)(MONOSODIUM/BI,ABEX OR
                 NA/BI,ABEX OR SODIUM/BI,ABEX) OR NSC259940/BI,ABEX OR NSC
                 259940/BI,ABEX
L46          802 SEA FILE=WPIX ABB=ON  LEVOTHYROXIN#/BI,ABEX OR THYROXIN#/BI,ABE
                 X
L47            2 SEA FILE=WPIX ABB=ON  ("LEVOTHYROXINE SODIUM"/CN OR LEVOTHYROXI
                 NE-SODIUM/CN)
L48          540 SEA FILE=WPIX ABB=ON  L47/DCR
L49          540 SEA FILE=WPIX ABB=ON  (RA11AM/DRN,DCN,DCRE OR R00050/DRN,DCN,DC
                 RE OR R04769/DRN,DCN,DCRE OR 0050/DRN,DCN,DCRE OR 108879-0-0-0/
                 DRN,DCN,DCRE OR 108879-2-0-0/DRN,DCN,DCRE)
L50         1021 SEA FILE=WPIX ABB=ON  (L49 OR L48 OR L46 OR L45)
L52            2 SEA FILE=WPIX ABB=ON  (L43 AND L44) OR ((L43 OR L44) AND L50)


FILE 'IPA' ENTERED AT 12:39:55 ON 23 FEB 2007
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FILE COVERS 1970 TO 15 FEB 2007 (20070215/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L63            2 SEA FILE=IPA ABB=ON  SCHREDER S?/AU
L64            0 SEA FILE=IPA ABB=ON  NISCHWITZ M?/AU
L65            2 SEA FILE=IPA ABB=ON  (L63 OR L64)


=> fil agricola pascal biotechno esbio lifesci drugb biosis vetu toxcenter anabstr
scisearch;d que l77
FILE 'AGRICOLA' ENTERED AT 12:40:06 ON 23 FEB 2007

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L5             1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L73           13 SEA SCHREDER S?/AU
L74            2 SEA NISCHWITZ M?/AU
L75        94695 SEA (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC 259940 OR
                 L5)
L77            2 SEA (L73 AND L74) OR ((L73 OR L74) AND L75)


=> dup rem l18,l38,l7,l65,l52,l35,l77
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FILE 'DRUGU' ENTERED AT 12:40:26 ON 23 FEB 2007
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PROCESSING COMPLETED FOR L18
PROCESSING COMPLETED FOR L38
PROCESSING COMPLETED FOR L7
PROCESSING COMPLETED FOR L65
PROCESSING COMPLETED FOR L52
PROCESSING COMPLETED FOR L35
PROCESSING COMPLETED FOR L77
L81           12 DUP REM L18 L38 L7 L65 L52 L35 L77 (9 DUPLICATES REMOVED)
```

ANSWERS '1-3' FROM FILE MEDLINE
ANSWER '4' FROM FILE DRUGU
ANSWERS '5-6' FROM FILE CAPLUS
ANSWERS '7-10' FROM FILE EMBASE
ANSWERS '11-12' FROM FILE BIOSIS

=> d iall 1-4; d ibib ed abs hitind 5-6; d iall 7-12

L81 ANSWER 1 OF 12 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2006142176 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 16246538
TITLE: Development of an in vitro/in vivo correlation for lipid formulations of EMD 50733, a poorly soluble, lipophilic drug substance.
AUTHOR: Schamp Karen; **Schreder Sven-Alexander**; Dressman Jennifer
CORPORATE SOURCE: Merck KGaA, Darmstadt, Germany.
SOURCE: European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, (2006 Apr) Vol. 62, No. 3, pp. 227-34. Electronic Publication: 2005-10-24.
Journal code: 9109778. ISSN: 0939-6411.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 14 Mar 2006
Last Updated on STN: 31 May 2006
Entered Medline: 30 May 2006

ABSTRACT:
PURPOSE: To develop lipid semisolid formulations of EMD 50733, a poorly soluble, neutral drug candidate and to develop an in vitro-in vivo correlation for these formulations using the dog as the in vivo model. METHODS: The model drug, EMD 50733, (with BCS Class II properties) was dissolved in molten lipid/surfactant mixtures and the melt was filled into hard capsules and allowed to re-solidify at room temperature. The dissolution profiles in bio-relevant dissolution media and the bioavailability in dogs were measured and compared to that of a standard formulation consisting of a lactose/drug mixture. RESULTS: The best results with respect to dissolution, stability upon storage and bioavailability were obtained with a formulation that contained a commercially available lipid mixture (Gelucire 44/14) and a solubilizing agent (2-vinylpyrrolidone). With this formulation it was possible to dissolve a typical drug dose in a fill volume suitable for a #0 capsule. Additionally, surface tension measurements showed that the formulation formed micelles during dissolution in aqueous media: the molecular dispersion of the drug in this self-micelle forming system is postulated to protect the drug from precipitation in vivo as well as in vitro. For other formulations tested, neither the in vitro nor the in vivo performance indicated sufficient drug solubilizing properties. CONCLUSION: To achieve adequate and reliable dissolution of poorly soluble drugs in vivo, lipid excipients should not only have appropriate solubilizing properties for the drug in the formulation, but should also assist in maintaining drug in solution during release in the GI tract.

CONTROLLED TERM:
Animals
Biological Availability
Capsules
Chemistry, Pharmaceutical
Chromatography, High Pressure Liquid
Dogs

Drug Carriers
Drug Stability
Drug Storage
Injections, Intravenous
Lactose
*Lipids: CH, chemistry
Liposomes
Polyethylene Glycols
Research Support, Non-U.S. Gov't
Solubility
Surface Tension
Vitamin E

CAS REGISTRY NO.: 121548-04-7 (gelucire 44-14); 1406-18-4 (Vitamin E); 63-42-3 (Lactose)

CHEMICAL NAME: 0 (Capsules); 0 (Drug Carriers); 0 (Lipids); 0 (Liposomes); 0 (Polyethylene Glycols)

L81 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2004305518 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15207542

TITLE: Degradation of raw or film-incorporated beta-cyclodextrin by enzymes and colonic bacteria.

AUTHOR: Fetzner Axel; Bohm Stefan; **Schreder Sven**; Schubert Rolf

CORPORATE SOURCE: Merck KGaA, Department of Pharmaceutical Development, Darmstadt, Germany.

SOURCE: European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V, (2004 Jul) Vol. 58, No. 1, pp. 91-7. Journal code: 9109778. ISSN: 0939-6411.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200501

ENTRY DATE: Entered STN: 24 Jun 2004
Last Updated on STN: 19 Jan 2005
Entered Medline: 18 Jan 2005

ABSTRACT:
beta-cyclodextrin (beta-CD) is a suitable excipient for peroral use, which improves the solubility of lipophilic drugs, as well as for colon-specific drug release when it is mixed with coating polymers. The first aim of this work was to examine the suitability of various enzymes as a simple in vitro model for the glycolytic activity in the human colon. alpha-Amylase (source Aspergillus oryzae) and taka diastase (source A. oryzae) showed remarkable degradation capacity of free beta-CD, whereas other alpha-amylases (sources Bacillus subtilis or Hog pancreas) were found to be unsuitable. The next aim was to find out if film-incorporated beta-CD is also degraded by these enzymes. Therefore, diffusion studies of 5-aminosalicylic acid (5-ASA) through Eudragit RS or Eudragit NE films containing beta-CD were performed with taka diastase present in the buffer medium. Pronounced diffusion of the drug through the Eudragit RS film was found only when swelling excipients like crosslinked sodium carboxymethylcellulose (CMC-CL sodium) or polyvinylpyrrolidone (PVP 25) were present in the film, indicating enhanced accessibility of beta-CD by the enzyme. Films containing CMC-CL without beta-CD showed even higher permeability, which also points to enzymatic degradation of CMC-CL. Permeabilization by taka diastase of Eudragit NE films without swelling agents correlated with the beta-CD content, whereas control films containing talcum remained impermeable upon enzyme action. Furthermore, the beta-CD degradation capacity of colonic bacteria like Escherichia fergusonii, Serratia odorifera or

Proteus mirabilis was examined with beta-CD coatings on tablets, which contained bisoprolol as a model drug. Tablets with beta-CD-containing Eudragit RS coatings showed the highest drug release upon incubation with P. mirabilis. The moderate drug release by E. fergusonii could be increased almost to the same level when the bacteria were pre-incubated for 24 h in medium containing 2.5 mg/ml beta-CD, indicating the induction of glycolytic enzymes by beta-CD in this colonic bacteria strain.

CONTROLLED TERM: Acrylic Resins: ME, metabolism
Animals
*Colon: EN, enzymology
*Colon: MI, microbiology
Diffusion
*Drug Carriers: ME, metabolism
Research Support, Non-U.S. Gov't
Swine
*beta-Cyclodextrins: ME, metabolism

CAS REGISTRY NO.: 33434-24-1 (Eudragit RS); 7585-39-9 (betadex)

CHEMICAL NAME: 0 (Acrylic Resins); 0 (Drug Carriers); 0 (beta-Cyclodextrins)

L81 ANSWER 3 OF 12 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 97418184 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9340022

TITLE: [Virtual endoscopy with post-processing helical CT data sets].
Virtuelle Endoskopie mittels Postprocessing helikaler CT-Datensatze.

AUTHOR: Dessl A; Giacomuzzi S M; Springer P; Stoeger A; Pototschnig C; Volklein C; **Schreder S G**; Jaschke W

CORPORATE SOURCE: Univ.-Klinik fur Radiologie, Innsbruck.

SOURCE: Aktuelle Radiologie, (1997 Jul) Vol. 7, No. 4, pp. 216-21.
Journal code: 9102962. ISSN: 0939-267X.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: German

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199710

ENTRY DATE: Entered STN: 5 Nov 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Oct 1997

ABSTRACT:
PURPOSE: The purpose of this work was to test a newly developed, post-processing software for virtual CT endoscopic methods. Virtual endoscopic images were generated from helical CT data sets in the region of the shoulder joint (n = 2), the tracheobronchial system (n = 3), the nasal sinuses (n = 2), the colon (n = 2), and the common carotid artery n = 1). Software developed specifically for virtual endoscopy ("Navigator") was used which, after a previous threshold value selection, makes the reconstruction of internal body surfaces possible by an automatic segmentation process. We have evaluated the usage of the software, the reconstruction time for individual images and sequences of images as well as the quality of the reconstruction. All pathological findings of the virtual endoscopy were confirmed by surgery. RESULTS: The post-processing program is easy to use and provides virtual endoscopic images within 50 seconds. Depending of the extent of the data set, virtual tracheobronchoscopy as a cine loop sequence required about 15 minutes. Through use of the threshold value-dependent surface reconstruction the demands on the computer configuration are limited; however, this also created quality problems in image calculation as a consequence of the accompanying loss of data. CONCLUSIONS: The Navigator software enables the calculation of virtual

endoscopic models with only moderate demands on the hardware.
CONTROLLED TERM: Artifacts
Bronchography
Carotid Artery, Common: RA, radiography
Colon: RA, radiography
*Endoscopes
English Abstract
Humans
*Image Processing, Computer-Assisted: IS, instrumentation
Paranasal Sinuses: RA, radiography
Sensitivity and Specificity
Shoulder Joint: RA, radiography
Software
*Tomography, X-Ray Computed: IS, instrumentation
Trachea: RA, radiography

L81 ANSWER 4 OF 12 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-28247 DRUGU G Full-text
TITLE: Surfactants used for polyacrylate-synthesis are decisive for drug release from thin films.
AUTHOR: **Schreder S**; Lee G
CORPORATE SOURCE: Univ.Heidelberg
LOCATION: Heidelberg, Germany,West
SOURCE: Eur.J.Pharm.Biopharm. (40, Suppl., 13S, 1994) 1 Ref.
AVAIL. OF DOC.: Institute for Pharmaceutical Technology and Biopharmaceutics, Heidelberg University, INF 366, D-69120 Heidelberg, Germany.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

Effects of different surfactants from the Antarox CO series used for synthesis of Eudragit NE30D on the release of the model drug, diazepam, from thin films were evaluated. Hydrophilic surfactants that have a high molecular weight were released slowly, while swelling was strongly influenced by their presence. Nevertheless, the rate of release of the lipophilic diazepam was only slightly increased. Lipophilic surfactants with a lower molecular weight were released in higher amounts and reached concentrations up to the CMC level. Drug liberation was much higher than that which could be explained by solubilization of the poorly water soluble diazepam. (congress abstract).

SECTION HEADING: G Galenics

CLASSIF. CODE: 29 Pharmaceutics
32 Psychotropic

CONTROLLED TERM:
RELEASE *FT; RATE *FT; SWELLING *FT; SOLUBILIZATION *FT; WETTABILITY *FT; FILM *FT
[01] DIAZEPAM *OC; DIAZEPAM *RN; LIPOPHILIC *FT; SEDATIVES *FT; RELAXANTS *FT; PSYCHOSEDATIVES *FT; TRANQUILIZERS *FT; BENZODIAZEPINE-AGONISTS *FT; OC *FT
CAS REGISTRY NO.: 439-14-5
[02] EUDRAGIT-NE-30D *OC; EUDRNE30D *RN; OC *FT
[03] SURFACTANT *FT; MOL. *FT; WEIGHT *FT; POLYMER *FT; PHENOL-ETHER *FT; ETHER *FT; ALCOHOL *FT; OC *FT
FIELD AVAIL.: AB; LA; CT; MPC
FILE SEGMENT: Literature

L81 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2000:31518 CAPLUS Full-text
DOCUMENT NUMBER: 132:83666
TITLE: Stabilized L-thyroxine preparation
INVENTOR(S): **Schreder, Sven; Nischwitz, Marion**
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 6 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19830246	A1	20000113	DE 1998-19830246	19980707
CA 2336748	A1	20000120	CA 1999-2336748	19990629
WO 2000002586	A1	20000120	WO 1999-EP4485	19990629
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9947793	A	20000201	AU 1999-47793	19990629
AU 751575	B2	20020822		
BR 9911884	A	20010327	BR 1999-11884	19990629
EP 1094841	A1	20010502	EP 1999-931209	19990629
EP 1094841	B1	20040818		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
HU 200104985	A2	20020429	HU 2001-4985	19990629
JP 2002520296	T	20020709	JP 2000-558845	19990629
AT 273697	T	20040915	AT 1999-931209	19990629
CZ 296897	B6	20060712	CZ 2001-74	19990629
NO 2001000089	A	20010105	NO 2001-89	20010105
US 6491946	B1	20021210	US 2001-743114	20010105
PRIORITY APPLN. INFO.:			DE 1998-19830246 A	19980707
			WO 1999-EP4485 W	19990629

ED Entered STN: 13 Jan 2000

AB A stable preparation for treatment of I deficiency goiter and prevention of goiter recurrence after resection contains L-thyroxine Na 5-400, KI 5-400 μg, microcryst. cellulose, and hydroxypropylmethylcellulose or gelatin as binder, and is free from antioxidants or other excipients. Release of L-thyroxine Na from the preparation was improved by use of this compound in micronized form (particle size 5-25 μm). Thus, an aqueous suspension of 5.25 g L-thyroxine Na was mixed with an aqueous solution of hydroxypropylmethylcellulose 175.00 and KI 6.54 g (total H2O amount 3259.00 g) and sprayed onto 4125.70 g microcryst. cellulose in a cyclone granulator. The granules were dried, sieved, mixed with croscarmellose Na 175.00 and Mg stearate 12.50 g and compressed to produce 50,000 tablets, each containing L-thyroxine Na 100 and KI 100 μg. These tablets were stable for ≥2 yr without development of a brown discoloration due to formation of I2.

IC ICM A61K033-18

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2
IT **55-03-8**, L-Thyroxine sodium 7681-11-0, Potassium iodide, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilized L-thyroxine preparation)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L81 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 1999:753040 CAPLUS Full-text
DOCUMENT NUMBER: 131:356126
TITLE: Pharmaceutical preparation containing levothyroxine sodium
INVENTOR(S): **Schreder, Sven; Nischwitz, Marion**
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9959551	A1	19991125	WO 1999-EP3087		19990505
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
DE 19821625	C1	20000105	DE 1998-19821625		19980515
CA 2333193	A1	19991125	CA 1999-2333193		19990505
AU 9939321	A	19991206	AU 1999-39321		19990505
AU 742382	B2	20020103			
BR 9910445	A	20010102	BR 1999-10445		19990505
EP 1077681	A1	20010228	EP 1999-922182		19990505
EP 1077681	B1	20021009			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
HU 200102125	A2	20011128	HU 2001-2125		19990505
JP 2002515421	T	20020528	JP 2000-549216		19990505
AT 225651	T	20021015	AT 1999-922182		19990505
PT 1077681	T	20030228	PT 1999-922182		19990505
ES 2184452	T3	20030401	ES 1999-922182		19990505
RU 2225711	C2	20040320	RU 2000-131588		19990505
SK 284155	B6	20041005	SK 2000-1689		19990505
TW 561058	B	20031111	TW 1999-88107870		19990514
NO 2000005758	A	20001114	NO 2000-5758		20001114
US 6646007	B1	20031111	US 2000-700421		20001115
IN 2000KN00621	A	20050311	IN 2000-KN621		20001211
ZA 2000007509	A	20020614	ZA 2000-7509		20001214
US 2004063611	A1	20040401	US 2003-661588		20030915
PRIORITY APPLN. INFO.:			DE 1998-19821625	A	19980515
			WO 1999-EP3087	W	19990505

US 2000-700421 A3 20001115

ED Entered STN: 26 Nov 1999

AB A pharmaceutical preparation containing micronized L-thyroxine Na, gelatin, and fillers is disclosed which is free of organic solvent residues. The preparation has improved stability and improved release of L-thyroxine in vitro. Thus, a solution of L-thyroxine Na 0.210 and gelatin 10.00 in H2O 56.66 kg was sprayed into a mixture of lactose monohydrate 131.80 and corn starch 50.00 kg in a fluidized bed granulator at 40-50°, and the granules were dried, sieved, mixed with croscarmellose Na 7.00 and Mg stearate 1.00, and compressed into tablets each containing 100 μg L-thyroxine.

IC ICM A61K009-20
ICS A61K031-195

CC 63-6 (Pharmaceuticals)

IT **55-03-8**, L-Thyroxine sodium 55-06-1, Liothyronine sodium
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical preparation containing levothyroxine sodium)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L81 ANSWER 7 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97241074 EMBASE Full-text
DOCUMENT NUMBER: 1997241074
TITLE: Recrystallization - Horror for shelf life specification?.
AUTHOR: **Schreder S.**; Schaffler A.
CORPORATE SOURCE: S. Schreder, MERCK KGaA, Pharmaceutical Development, 64271 Darmstadt, Germany
SOURCE: Proceedings of the Controlled Release Society, (1997) No. 24, pp. 453-454. .
Refs: 6
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
ENTRY DATE: Entered STN: 4 Sep 1997
Last Updated on STN: 4 Sep 1997
CONTROLLED TERM: Medical Descriptors:
*crystallization
conference paper
controlled study
drug delivery system
drug quality
drug solubility
drug stability
physical chemistry
shelf life
temperature
Drug Descriptors:
*eudragit: PR, pharmaceutics
aerosil
clonidine: PR, pharmaceutics
surfactant

CAS REGISTRY NO.: (eudragit) 24938-16-7, 51822-44-7, 9065-11-6; (clonidine) 4205-90-7, 4205-91-8, 57066-25-8

L81 ANSWER 8 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 96272085 EMBASE Full-text
DOCUMENT NUMBER: 1996272085
TITLE: Water - A plastizicer for polymers?.
AUTHOR: **Schreder S.**; Lee G.
CORPORATE SOURCE: Merck KGaA, Pharmaceutical Development,64271 Darmstadt, Germany
SOURCE: Proceedings of the Controlled Release Society, (1996) No. 23, pp. 727-728. .
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 030 Pharmacology
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Nov 1996
Last Updated on STN: 12 Nov 1996
CONTROLLED TERM: Medical Descriptors:
*drug release
biodegradation
conference paper
temperature
water absorption
Drug Descriptors:
*plasticizer
*polymer
*water
eudragit
octoxinol
surfactant
CAS REGISTRY NO.: (water) 7732-18-5; (eudragit) 24938-16-7, 51822-44-7, 9065-11-6; (octoxinol) 9002-93-1

L81 ANSWER 9 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 95274652 EMBASE Full-text
DOCUMENT NUMBER: 1995274652
TITLE: Plastifying effect of surfactants - Decisive for drug release.
AUTHOR: **Schreder S.**; Lee G.
CORPORATE SOURCE: Inst. for Pharmaceutical Technology, Biopharmaceutics, Heidelberg University,Heidelberg, Germany
SOURCE: Proceedings of the Controlled Release Society, (1995) No. 22, pp. 398-399. .
ISSN: 1022-0178 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Oct 1995
Last Updated on STN: 3 Oct 1995
CONTROLLED TERM: Medical Descriptors:
*drug diffusion
*drug release

conference paper
hydrophilicity
lipophilicity
plasticity
drug delivery system
Drug Descriptors:
*eudragit
*plasticizer
*surfactant
diazepam: PR, pharmaceutics
diazepam: PK, pharmacokinetics
octoxinol
paracetamol: PR, pharmaceutics
paracetamol: PK, pharmacokinetics
polyacrylic acid
CAS REGISTRY NO.: (eudragit) 24938-16-7, 51822-44-7, 9065-11-6; (diazepam) 439-14-5; (octoxinol) 9002-93-1; (paracetamol) 103-90-2; (polyacrylic acid) 74350-43-9, 87003-46-1, 9003-01-4, 9003-04-7

L81 ANSWER 10 OF 12 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 94367819 EMBASE Full-text
DOCUMENT NUMBER: 1994367819
TITLE: The complex effects of surfactant on drug release from thin films.
AUTHOR: **Schreder S.**; Lee G.
CORPORATE SOURCE: Institute Pharmaceutical Technology, Biopharmaceutics, Heidelberg University,Heidelberg, Germany
SOURCE: Proceedings of the Controlled Release Society, (1994) No. 21, pp. 678-679. .
ISSN: 1076-0458 CODEN: 58GMAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Dec 1994
Last Updated on STN: 21 Dec 1994
CONTROLLED TERM: Medical Descriptors:
*drug release
conference paper
controlled study
drug diffusion
drug solubility
film
lipophilicity
Drug Descriptors:
*surfactant
diazepam: PR, pharmaceutics
eudragit
CAS REGISTRY NO.: (diazepam) 439-14-5; (eudragit) 24938-16-7, 51822-44-7, 9065-11-6

L81 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:18365 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400020978

TITLE: Process for preparing a pharmaceutical formulation containing **levothyroxine** sodium.
AUTHOR(S): **Schreder, Sven** [Inventor, Reprint Author]; **Nischwitz, Marion** [Inventor]
CORPORATE SOURCE: Heidelberg, Germany
ASSIGNEE: Merck Patent GmbH, Darmstadt, Germany
PATENT INFORMATION: US 6646007 20031111
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov 11 2003) Vol. 1276, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Dec 2003
Last Updated on STN: 24 Dec 2003
ABSTRACT:The invention relates to a pharmaceutical preparation comprising ***levothyroxine*** sodium, gelatin and fillers, which is free of organic solvent residues.
NAT. PATENT. CLASSIF.:514567000
CONCEPT CODE: Pathology - Therapy 12512
Pharmacology - General 22002
INDEX TERMS: Major Concepts
Methods and Techniques; Pharmaceuticals (Pharmacology)
INDEX TERMS: Methods & Equipment
levothyroxine sodium pharmaceutical formulation preparation process: laboratory techniques

L81 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:68555 BIOSIS Full-text
DOCUMENT NUMBER: PREV200300068555
TITLE: Pharmaceutical **levothyroxine** preparation.
AUTHOR(S): **Schreder, Sven** [Inventor, Reprint Author]; **Nischwitz, Marion** [Inventor]
CORPORATE SOURCE: Heidelberg, Germany
ASSIGNEE: Merck Patent Gesellschaft, Darmstadt, Germany
PATENT INFORMATION: US 6491946 20021210
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Dec 10 2002) Vol. 1265, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jan 2003
Last Updated on STN: 29 Jan 2003
ABSTRACT:The invention relates to a pharmaceutical preparation comprising ***levothyroxine*** sodium, potassium iodide, microcrystalline cellulose and binding agent, which is free of antioxidants or further auxiliaries, and processes for its production.
NAT. PATENT. CLASSIF.:424465000
CONCEPT CODE: Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Carbohydrates 10068
Pathology - Therapy 12512
Pharmacology - General 22002
Pharmacology - Endocrine system 22016
Chemotherapy - General, methods and metabolism 38502
Chemotherapy - Antifungal agents 38508
INDEX TERMS: Major Concepts
Pharmacology

INDEX TERMS: Chemicals & Biochemicals
binding agent; **levothyroxine**: hormone-drug, pharmaceutical preparation; **levothyroxine** sodium: antihypothyroid-drug; microcrystalline cellulose; potassium iodide: antifungal-drug, antiinfective-drug

INDEX TERMS: Methods & Equipment
pharmaceutical synthesis: laboratory techniques

REGISTRY NUMBER: 51-48-9 (**levothyroxine**)
55-03-8 (**levothyroxine** sodium)
7681-11-0 (potassium iodide)

TEXT SEARCH

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=> => fil capl; d que l12
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FILE LAST UPDATED: 22 Feb 2007  (20070222/ED)

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L5            1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L6          488 SEA FILE=CAPLUS ABB=ON  L5
L9        41163 SEA FILE=CAPLUS ABB=ON  GELATIN#/OBI
L11        6587 SEA FILE=CAPLUS ABB=ON  L9(L)(PAC OR PKT OR DMA OR THU)/RL
L12          10 SEA FILE=CAPLUS ABB=ON  L11 AND L6


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L82           8 L12 NOT L7

=> fil embase; d que l34; fil drugu; d que l42

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 FILE COVERS 1974 TO 23 Feb 2007 (20070223/ED)

 EMBASE is now updated daily.  SDI frequency remains weekly (default)
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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L5            1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L26        1269 SEA FILE=EMBASE ABB=ON  L5
L27        1268 SEA FILE=EMBASE ABB=ON  LEVOTHYROXINE SODIUM/CT
L29        6703 SEA FILE=EMBASE ABB=ON  GELATIN/CT
L32       13468 SEA FILE=EMBASE ABB=ON  GELATIN#
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L34             0 SEA FILE=EMBASE ABB=ON  (L26 OR L27) AND (L29 OR L32)


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FILE LAST UPDATED: 23 FEB 2007        <20070223/UP>
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>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<



L5              1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L39           439 SEA FILE=DRUGU ABB=ON  L5
L40          1142 SEA FILE=DRUGU ABB=ON  LEVOTHYROXINE SODIUM/CT
L41          3909 SEA FILE=DRUGU ABB=ON  GELATIN#
L42             0 SEA FILE=DRUGU ABB=ON  (L39 OR L40) AND L41


=> fil wpix; d que l62

FILE 'WPIX' ENTERED AT 12:43:31 ON 23 FEB 2007
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FILE LAST UPDATED:                    19 FEB 2007   <20070219/UP>
MOST RECENT THOMSON SCIENTIFIC UPDATE:     200712      <200712/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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    loaded into the database during January 2007.
    There will not be any update date (UP) written for the reclassified
    documents, but they can be identified by 20060101/UPIC. <<<

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http://www.stn-international.de/training_center/patents/stn_guide.pdf

FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf


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http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

>>> New and revised Manual Codes went live in Derwent World Patents Index
    To view the lists of new, revised and retired codes for both CPI and
    EPI,  please go to:
    http://scientific.thomson.com/dwpi-manualcoderevision <<<
'BI ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE
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L45          72 SEA FILE=WPIX ABB=ON  (LEVOTHYROXINE/BI,ABEX OR (LEVO/BI,ABEX
                OR L/BI,ABEX)(W)THYROXINE/BI,ABEX)(1A)(MONOSODIUM/BI,ABEX OR
                NA/BI,ABEX OR SODIUM/BI,ABEX) OR NSC259940/BI,ABEX OR NSC
                259940/BI,ABEX
L46         802 SEA FILE=WPIX ABB=ON  LEVOTHYROXIN#/BI,ABEX OR THYROXIN#/BI,ABE
                X
L47           2 SEA FILE=WPIX ABB=ON  ("LEVOTHYROXINE SODIUM"/CN OR LEVOTHYROXI
                NE-SODIUM/CN)
L48         540 SEA FILE=WPIX ABB=ON  L47/DCR
L49         540 SEA FILE=WPIX ABB=ON  (RA11AM/DRN,DCN,DCRE OR R00050/DRN,DCN,DC
                RE OR R04769/DRN,DCN,DCRE OR 0050/DRN,DCN,DCRE OR 108879-0-0-0/
                DRN,DCN,DCRE OR 108879-2-0-0/DRN,DCN,DCRE)
L50        1021 SEA FILE=WPIX ABB=ON  (L49 OR L48 OR L46 OR L45)
L51       34560 SEA FILE=WPIX ABB=ON  GELATIN#/BI,ABEX
L53          41 SEA FILE=WPIX ABB=ON  L50 AND L51
L55       15426 SEA FILE=WPIX ABB=ON  ?ASSAY?/TI
L56      199868 SEA FILE=WPIX ABB=ON  MEASURING/TI
L60       14807 SEA FILE=WPIX ABB=ON  ANALYZING/TI
L61       61970 SEA FILE=WPIX ABB=ON  SIMULTANEOUS?/TI
L62          30 SEA FILE=WPIX ABB=ON  L53 NOT (L55 OR L56 OR L60 OR L61)


=> s l62 not l52

L83          28 L62 NOT L52

=> fil ipa; d que l69

FILE 'IPA' ENTERED AT 12:43:35 ON 23 FEB 2007
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FILE COVERS 1970 TO 15 FEB 2007 (20070215/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.


L5            1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L66           1 SEA FILE=IPA ABB=ON  L5
L67         798 SEA FILE=IPA ABB=ON  (LEVOTHYROXINE OR THYROXINE) OR NSC259940
                OR NSC 259940
L68        1409 SEA FILE=IPA ABB=ON  GELATIN#
L69           0 SEA FILE=IPA ABB=ON  (L66 OR L67) AND L68


=> fil agricola pascal biotechno esbio lifesci drugb biosis vetu toxcenter anabstr
scisearch;d que l80

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FILE 'PASCAL' ENTERED AT 12:43:36 ON 23 FEB 2007
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FILE 'SCISEARCH' ENTERED AT 12:43:36 ON 23 FEB 2007
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L5             1 SEA FILE=REGISTRY ABB=ON  "LEVOTHYROXINE SODIUM"/CN
L75        94695 SEA (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC 259940 OR
                 L5)
L76        57422 SEA GELATIN#
L78           54 SEA L75 AND L76
L80            8 SEA L78 AND (SLAUGHTER? OR WOUND OR PHOTOSENSITIVE OR PARENTERA
                 L OR PHARMACEUTICAL OR MEDICAMENTS)/TI


=> s l80 not l77

L84            7 L80 NOT L77

=> fil medl; d que l20

FILE 'MEDLINE' ENTERED AT 12:43:43 ON 23 FEB 2007

 FILE LAST UPDATED: 22 Feb 2007 (20070222/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


L13        28884 SEA FILE=MEDLINE ABB=ON  THYROXINE/CT
L14         5986 SEA FILE=MEDLINE ABB=ON  GELATIN/CT
L19         9914 SEA FILE=MEDLINE ABB=ON  L13(L)(AD OR PD OR PK OR TU)/CT
L20            2 SEA FILE=MEDLINE ABB=ON  L19 AND L14
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L85          2 L20 NOT L18

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FILE 'MEDLINE' ENTERED AT 12:44:24 ON 23 FEB 2007

FILE 'CAPLUS' ENTERED AT 12:44:24 ON 23 FEB 2007
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FILE 'SCISEARCH' ENTERED AT 12:44:24 ON 23 FEB 2007
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PROCESSING COMPLETED FOR L85
PROCESSING COMPLETED FOR L82
PROCESSING COMPLETED FOR L83
PROCESSING COMPLETED FOR L84
L86          40 DUP REM L85 L82 L83 L84 (5 DUPLICATES REMOVED)
                ANSWERS '1-2' FROM FILE MEDLINE
                ANSWERS '3-10' FROM FILE CAPLUS
                ANSWERS '11-35' FROM FILE WPIX
                ANSWERS '36-39' FROM FILE TOXCENTER
                ANSWER '40' FROM FILE SCISEARCH

=> d iall 1-2; d ibib ed abs hitind 3-10; d iall abeq tech hit hitstr 11-35; d iall
36-40; fil hom

L86  ANSWER 1 OF 40     MEDLINE on STN                  DUPLICATE 4
ACCESSION NUMBER:   95283720     MEDLINE  Full-text
DOCUMENT NUMBER:    PubMed ID: 7766319
TITLE:              Serum-free cell culture medium induces acceleration of
                    wound healing in guinea-pigs.
AUTHOR:             Lindenbaum E S; Tendler M; Beach D
CORPORATE SOURCE:   Morphology Research Unit, Bruce Rappaport Faculty of
                    Medicine, Technion IIT, Haifa, Israel.
SOURCE:             Burns : journal of the International Society for Burn
                    Injuries, (1995 Mar) Vol. 21, No. 2, pp. 110-5.
                    Journal code: 8913178. ISSN: 0305-4179.
PUB. COUNTRY:       ENGLAND: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199506
ENTRY DATE:         Entered STN: 13 Jul 1995
                    Last Updated on STN: 6 Feb 1998
                    Entered Medline: 30 Jun 1995
ABSTRACT:
Among the current methods employed in the treatment of wounds, a moist dressing
is considered to be the optimal environment for the process of healing thereby
avoiding dessication of the wound bed.  This study is based on the hypothesis
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that wound cell proliferation is dependent not only on moisture but also upon the composition of the moist microenvironment in the wound. That composition in turn is formed by diffusion of nutrients from the existing vascular bed in and around the wound as well as by the wound cells' cellular products. Since in wounds the impaired vascular supply causes tissue deprivation, a continuous supply of nutrients and hormones will create an optimal substrate for cellular mitogenic activity, synthesis of matrix, growth factors and cytokines leading to wound healing. Modified serum-free cell culture medium was supplemented with non-steroidal anabolic hormones: growth hormone, thyroxin and insulin, transferrin and sodium selenite. The medium was prepared in a 1 per cent alginate gel matrix. Under general anaesthesia with ketamine (Imalgene 1000, Rhone Merieux, France) four 2 x 2 cm full-thickness skin patches were surgically extirpated from the dorsum of Hartley-derived guinea-pigs. Each experimental group consisted of seven animals, i.e. 28 wounds that received the same treatment. Compositions of gelatin in saline, agarose in saline, agarose in medium and agarose in saline supplemented with the three hormones were compared to agarose in medium supplemented with the three hormones. After application of the gel (1 ml/cm2), the wounds were dressed with gauze, elastic adhesive bandage and netting.(ABSTRACT TRUNCATED AT 250 WORDS)

CONTROLLED TERM: Analysis of Variance
Animals
Cells, Cultured
Comparative Study
Culture Media, Serum-Free
Drug Combinations
Gelatin: PD, pharmacology
Gels
Growth Hormone: PD, pharmacology
Guinea Pigs
Insulin: PD, pharmacology
Regression Analysis
Research Support, Non-U.S. Gov't
Sepharose: PD, pharmacology
*Skin: DE, drug effects
*Skin: IN, injuries
Skin Physiology
Sodium Selenite: PD, pharmacology
Thyroxine: PD, pharmacology
Transferrin: PD, pharmacology
*Wound Healing: DE, drug effects

CAS REGISTRY NO.: 10102-18-8 (Sodium Selenite); 11061-68-0 (Insulin); 11096-37-0 (Transferrin); 7488-70-2 (Thyroxine); 9000-70-8 (Gelatin); 9002-72-6 (Growth Hormone); 9012-36-6 (Sepharose)

CHEMICAL NAME: 0 (Culture Media, Serum-Free); 0 (Drug Combinations); 0 (Gels)

L86 ANSWER 2 OF 40 MEDLINE on STN
ACCESSION NUMBER: 68230826 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 4296672
TITLE: Effect of hormones on ceruloplasmin and copper concentrations in the plasma of the rat.
AUTHOR: Evans G W; Wiederanders R E
SOURCE: The American journal of physiology, (1968 May) Vol. 214, No. 5, pp. 1152-4.
Journal code: 0370511. ISSN: 0002-9513.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 196806
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 25 Jun 1968
CONTROLLED TERM: Check Tags: Female; Male
*Adrenal Glands: PH, physiology
Adrenalectomy
Age Factors
Animals
Animals, Newborn
*Ceruloplasmin: BL, blood
*Copper: BL, blood
*Corticotropin: PD, pharmacology
*Cortisone: PD, pharmacology
Gelatin
Injections, Subcutaneous
Melanocyte-Stimulating Hormones: PD, pharmacology
Rats
***Thyroxine: PD, pharmacology**
CAS REGISTRY NO.: 53-06-5 (Cortisone); 7440-50-8 (Copper); 7488-70-2 (Thyroxine); 9000-70-8 (Gelatin); 9002-60-2 (Corticotropin); 9002-79-3 (Melanocyte-Stimulating Hormones)
CHEMICAL NAME: EC 1.16.3.1 (Ceruloplasmin)

L86 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:494109 CAPLUS Full-text
DOCUMENT NUMBER: 144:495380
TITLE: Dry powder comprising levothyroxine sodium administered via inhalator
INVENTOR(S): Tseti, Ioulia
PATENT ASSIGNEE(S): Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., Greece
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006054120	A1	20060526	WO 2004-GR55	20041118

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: WO 2004-GR55 20041118
ED Entered STN: 26 May 2006

AB Dosol. of thyroid hormone using a suitable device is claimed. Composition of 100 mg of dry powder comprised levothyroxine sodium hydrate 0.233 mg (5% excess), lactose particles 91.767, and sodium starch glycolate 5 mg.
CC 63-6 (Pharmaceuticals)
IT **Gelatins**, biological studies
Thyroid hormones
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(dry powder comprising levothyroxine sodium administered via inhalator)
IT **55-03-8**, Levothyroxine sodium 63-42-3, Lactose 557-04-0, Magnesium stearate 7631-86-9, Silicon dioxide, biological studies 9003-39-8, Polyvinylpyrrolidone 9063-38-1, Sodium Starch glycolate 64044-51-5
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dry powder comprising levothyroxine sodium administered via inhalator)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 4 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2005:1154357 CAPLUS Full-text
DOCUMENT NUMBER: 143:411088
TITLE: Method for administering medicaments to subjects with swallowing difficulties and disorders
INVENTOR(S): Soltero, Richard
PATENT ASSIGNEE(S): Soltero, Richard, USA
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005099670	A1	20051027	WO 2005-US9548	20050324

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-558349P P 20040331
ED Entered STN: 28 Oct 2005
AB The present invention provides a solid dosage form that facilitates swallowing comprising a hydrated polymeric gelatinous matrix, one or more active ingredients, and optionally one or more excipients. The second embodiment of the invention is a method for administering to a patient a solid dosage form that facilitates swallowing comprising a hydrated polymeric matrix, one or more active ingredients, and optionally one or more excipients without water or other fluids needed to facilitate swallowing.
IC ICM A61K009-10
ICS A61K009-20; A61K035-78; A61K047-38; A61K047-42
CC 63-6 (Pharmaceuticals)
IT **Gelatins**, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(hydrated type A, hydrated type B; method for administering medicaments

to subjects with swallowing difficulties and disorders)

IT 50-48-6, Amitriptyline 50-78-2, Acetyl salicylic acid 50-81-7, Ascorbic acid, biological studies 55-03-8, Levothyroxine sodium 58-85-5, Biotin 59-30-3, Folic acid, biological studies 68-19-9, Vitamin B12 77-19-0, Dicyclomine 83-88-5, Riboflavin, biological studies 98-92-0, Niacinamide 103-90-2, Acetaminophen 127-47-9, Vitamin A acetate 137-08-6, Calcium pantothenate 141-01-5, Ferrous fumarate 303-49-1, Clomipramine 315-30-0, Allopurinol 318-98-9, Propranolol hydrochloride 471-34-1, Calcium carbonate, biological studies 532-43-4 657-24-9, Metformin 1309-48-4, Magnesium oxide, biological studies 1314-13-2, Zinc oxide, biological studies 1317-38-0, Cupric oxide, biological studies 1344-00-9, Sodium aluminum silicate 1406-16-2, Vitamin D 1406-18-4, Vitamin E 7235-40-7, Beta-carotene 7439-93-2, Lithium, biological studies 7447-40-7, Potassium chloride, biological studies 7631-95-0, Sodium molybdate 7681-11-0, Potassium iodide, biological studies 7772-99-8, Stannous chloride, biological studies 7786-81-4, Nickelous sulfate 8059-24-3, Vitamin B6 9000-69-5, Pectin 9002-18-0, Agar 9004-61-9, Hyaluronic acid 9004-64-2, Hydroxypropyl cellulose. 10025-73-7, Chromium chloride (CrCl3) 11104-38-4, Vitamin K1 13410-01-0, Sodium selenate 13718-26-8, Sodium metavanadate 15687-27-1, Ibuprofen 21829-25-4, Nifedipine 25322-68-3, Polyethylene oxide. 28981-97-7, Alprazolam 29122-68-7, Atenolol 36894-69-6, Labetalol 37353-59-6, Hydroxymethyl cellulose. 42399-41-7, Diltiazem 62571-86-2, Captopril
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for administering medicaments to subjects with swallowing difficulties and disorders)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 5 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2002:51198 CAPLUS Full-text
DOCUMENT NUMBER: 136:107522
TITLE: Thyroid hormone solid dosage forms
INVENTOR(S): Murari, Ramaswamy; Chrai, Suggy S.
PATENT ASSIGNEE(S): Delsys Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003914	A2	20020117	WO 2001-US21422	20010706
WO 2002003914	A3	20020606		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2415080	A1	20020117	CA 2001-2415080	20010706
AU 2001071875	A5	20020121	AU 2001-71875	20010706
US 2002077364	A1	20020620	US 2001-900094	20010706
EP 1296666	A2	20030402	EP 2001-950930	20010706

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

HU 200301416	A2	20030929	HU 2003-1416		20010706
JP 2004502708	T	20040129	JP 2002-508371		20010706
PRIORITY APPLN. INFO.:			US 2000-216275P	P	20000706
			WO 2001-US21422	W	20010706

ED Entered STN: 18 Jan 2002

AB A method is disclosed for formulating a solid dosage of thyroid hormone, while avoiding instability caused by interaction of the active ingredient with excipients. The thyroid hormone may be levothyroxine sodium or triiodothyronine. The method comprises depositing the active ingredient, preferably electrostatically, as a dry powder substantially free of excipients, onto a pharmaceutically acceptable polymer substrate. Levothyroxine Na was deposited onto a polymer film formulated with HPMC and hydroxypropyl cellulose with PEG 400.

IC ICM A61K

CC 63-6 (Pharmaceuticals)

IT Acrylic polymers, biological studies
Gelatins, biological studies
Polysaccharides, biological studies
RL: MOA (Modifier or additive use); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(thyroid hormone solid dosage forms)

IT **55-03-8**, Levothyroxine sodium 6893-02-3, Triiodothyronine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thyroid hormone solid dosage forms)

L86 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:904666 CAPLUS Full-text

DOCUMENT NUMBER: 145:278358

TITLE: Medicine composition containing thyroid hormone for oral administration

INVENTOR(S): Garawane, Albit; Migeori, Moriqao; Dematino, Alexander; Achnagria, Angel Mateor

PATENT ASSIGNEE(S): A'Ertegong Company, Switz.

SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 26pp.
CODEN: CNXXEV

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1820783	A	20060823	CN 2005-10007407	20050217
PRIORITY APPLN. INFO.:			CN 2005-10007407	20050217

ED Entered STN: 05 Sep 2006

AB The title medicine composition comprises thyroid hormone or salts of thyroid hormone, and gelatin (preferable). This medicine composition has a form of uniform soft gel matrix that can be swallowed, so this medicine composition is safe and stable for oral administration.

CC 63-6 (Pharmaceuticals)

IT **Gelatins**, biological studies
Polyoxyalkylenes, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(medicine composition containing thyroid hormone for oral administration)

IT 51-48-9, Levothyroxine, biological studies **55-03-8**, Levothyroxine sodium 55-06-1 6893-02-3, Triiodothyronine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(medicine composition containing thyroid hormone for oral administration)

L86 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:904667 CAPLUS Full-text
DOCUMENT NUMBER: 145:278359
TITLE: Manufacture of oral thyroid hormone soft gel for treating thyroid dysfunction
INVENTOR(S): Dematino, Alexander; Achnagria, Angel Mateor; Garawane, Albit; Migeori, Moriqao
PATENT ASSIGNEE(S): A'Ertegong Company, Switz.
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 73pp. CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1820782	A	20060823	CN 2005-10007403	20050217
PRIORITY APPLN. INFO.:			CN 2005-10007403	20050217

ED Entered STN: 05 Sep 2006
AB The title oral thyroid hormone soft gel contains (by weight%) thyroid hormone (T3 and/orT4, or their salts) 0.001-1, gelatin 30-68 (produced from cattle, pig or fish), glycerol 31-60, and water 1-10 (all calculated by dry weight). The soft gel has a shape and size of tablet or capsule. The agent can be used for treating thyroid dysfunction, and has the advantages of high safety and stability.
CC 63-6 (Pharmaceuticals)
IT **Gelatins**, biological studies
Polyoxyalkylenes, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(manufacture of oral thyroid hormone soft gel for treating thyroid dysfunction)
IT 51-48-9, Levothyroxine, biological studies **55-03-8**, Levothyroxine sodium 6893-02-3, Triiodothyronine
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of oral thyroid hormone soft gel for treating thyroid dysfunction)

L86 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:201474 CAPLUS Full-text
DOCUMENT NUMBER: 138:226748
TITLE: Pharmaceutical formulations for thyroid hormones
INVENTOR(S): Garavani, Alberto; Marchiorri, Maurizio; Di Martino, Alessandro; Mateo Echanagorria, Angel
PATENT ASSIGNEE(S): Altergon S.A., Switz.
SOURCE: Eur. Pat. Appl., 12 pp. CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1291021	A2	20030312	EP 2002-14594	20020702
EP 1291021	A3	20030416		
EP 1291021	B1	20051214		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

CA 2392545	A1	20030102	CA 2002-2392545	20020628
US 2003050344	A1	20030313	US 2002-188467	20020702
JP 2003081870	A	20030319	JP 2002-193024	20020702
AT 312621	T	20051215	AT 2002-14594	20020702
ES 2254559	T3	20060616	ES 2002-2014594	20020702
KR 2006087618	A	20060803	KR 2005-8307	20050129
KR 2006087619	A	20060803	KR 2005-8308	20050129

PRIORITY APPLN. INFO.: IT 2001-MI1401 A 20010702

ED Entered STN: 14 Mar 2003

AB The present invention provides for pharmaceutical formulations based on thyroid hormones enabling a stable oral administration in the framework of the strict therapeutic index prescribed in the case of thyroid disorders. Thus, a capsule formulation contained T3 Na 0.001-1, glycerol 5-30, EtOH 1-15, PEG-400 20-90, gelatin 3-40, water 1-10, and 85% solution of sorbitol/sorbitan 0.5-30%.

IC ICM A61K038-24
ICS A61K009-48

CC 63-6 (Pharmaceuticals)

IT **Gelatins**, biological studies
Polyoxyalkylenes, biological studies
Thyroid hormones
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(pharmaceutical formulations for thyroid hormones)

IT 51-48-9, T4, biological studies **55-03-8** 55-06-1 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 64-17-5, Ethanol, biological studies 6893-02-3, T3 9004-65-3, Hydroxypropyl methyl cellulose 9004-67-5, Methyl cellulose 9005-35-0, Calcium alginate 9005-64-5, Polysorbate 20 9005-65-6, Tween 80 25322-68-3, Polyethylene glycol 31692-85-0, Glycofurol
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulations for thyroid hormones)

L86 ANSWER 9 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:51244 CAPLUS Full-text
DOCUMENT NUMBER: 136:123634
TITLE: Method for formulating health products with enhanced stability
INVENTOR(S): Murari, Ramaswamy; Katdare, Ashok; Chrai, Suggy S.; Harmon, Troy M.
PATENT ASSIGNEE(S): Delsys Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003965	A1	20020117	WO 2001-US21418	20010706

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2415082	A1	20020117	CA 2001-2415082		20010706
EP 1296653	A1	20030402	EP 2001-952487		20010706
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
HU 200301415	A2	20030929	HU 2003-1415		20010706
JP 2004502724	T	20040129	JP 2002-508420		20010706
US 2005013924	A1	20050120	US 2003-332255		20030814
PRIORITY APPLN. INFO.:			US 2000-216205P	P	20000706
			WO 2001-US21418	W	20010706

ED Entered STN: 18 Jan 2002

AB A method is disclosed for formulating health products, including solid pharmaceutical compns., while avoiding instability caused by an interaction of the active ingredient with excipients. The method comprises the steps of selecting an active ingredient that loses stability or potency upon interaction with pharmaceutical excipients and depositing the active ingredient, preferably electrostatically, as a dry powder substantially free of excipients, onto a pharmaceutically acceptable polymer substrate. The compatibility of various conventional polymer films with levothyroxine sodium was evaluated. The goal was to select a suitable polymer film to maximize the stability of levothyroxine sodium for electrostatic deposition, and to develop a dosage form using selected polymer films. Five of the 8 polymer film formulations (e.g., Et cellulose and HPMC) were associated with a loss of no more than 2% of the active ingredient under stress conditions.

IC ICM A61K009-20
ICS A61K009-28; A61K009-14; B05D001-04

CC 63-6 (Pharmaceuticals)

IT Acrylic polymers, biological studies
Gelatins, biological studies
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polysaccharides, biological studies
Steroids, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(formulating health products with enhanced stability)

IT **55-03-8**, Levothyroxine sodium 55-63-0, Nitroglycerin 79-41-4D, Methacrylic acid, esters, polymers 88-99-3D, Phthalic acid, polymers 6452-71-7, Oxprenolol 9000-11-7, Carboxymethyl cellulose 9000-69-5, Pectin 9002-89-5, Poly(vinyl alcohol) 9003-20-7, Poly(vinyl acetate) 9003-39-8, PVP 9004-10-8, Insulin, biological studies 9004-38-0, Cellulose acetate phthalate 9004-57-3, Ethyl cellulose 9004-62-0, Hydroxyethyl cellulose 9004-64-2, Hydroxypropyl cellulose 9004-65-3, HPMC 9004-67-5, Methyl cellulose 9005-25-8D, Starch, derivs. 9005-49-6, Heparin, biological studies 9005-65-6, Polysorbate 80 21829-25-4, Nifedipine 25322-68-3, Polyethylene glycol 25717-80-0, Molsidomine 77518-07-1, Astra FLA 336 99614-02-5, Ondansetron 103577-45-3, Lansoprazole 103775-10-6, Moexipril 123948-87-8, Topotecan
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(formulating health products with enhanced stability)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L86 ANSWER 10 OF 40 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:754992 CAPLUS Full-text
DOCUMENT NUMBER: 137:253046
TITLE: Process for preparing solid dosage forms for unpalatable pharmaceuticals
INVENTOR(S): Yarwood, Richard J.; Kearney, Patrick; Thompson, Andrew R.

PATENT ASSIGNEE(S): R.P. Scherer Technologies, Inc., UK
SOURCE: U.S. Pat. Appl. Publ., 7 pp., Cont.-in-part of U.S. Ser. No. 26,561, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002142038	A1	20021003	US 2000-551361	20000418
US 6726928	B2	20040427		
US 5738875	A	19980414	US 1994-330936	19941028
US 2004028730	A1	20040212	US 2003-635710	20030805
PRIORITY APPLN. INFO.:			US 1994-330936	A1 19941028
			US 1998-26561	B2 19980220
			US 2000-551361	B1 20000418

ED Entered STN: 04 Oct 2002
AB A process for the preparation of a rapidly disintegrating dosage form a pharmaceutically active substance which has an unacceptable taste wherein there is formed a solution or a suspension in a solvent of a form of the pharmaceutically active substance which is less soluble in water and more palatable than the form with the unacceptable taste together with a water-soluble or water-dispersible carrier material. Discrete units of the suspension or solution are formed and the solvent is removed from the discrete units under conditions whereby a network of the carrier material carrying a dosage for the less soluble and more palatable form of the pharmaceutically active substance is formed. Thus, a formulation contained loperamide-HCl 12, NaHCO3 2.5, gelatin 35, mannitol 26, and water 825.5 g.
IC ICM A61K009-14
INCL 424486000
CC 63-6 (Pharmaceuticals)
IT **Gelatins**, biological studies
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(process for preparation of solid dosage forms for unpalatable pharmaceuticals)
IT **55-03-8**, Thyroxine sodium 15307-81-0, Diclofenac Potassium 34552-83-5, Loperamide hydrochloride 53179-11-6, Loperamide 57808-66-9, Domperidone
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(process for preparation of solid dosage forms for unpalatable pharmaceuticals)

L86 ANSWER 11 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-136071 [14] WPIX
CROSS REFERENCE: 2006-087378
DOC. NO. CPI: C2006-046773 [14]
TITLE: Hydrogel useful in delivering biologically active group, e.g. adenosine deaminase and agalsidase comprises several opening pores comprising reversible prodrug linkers for covalently linking the hydrogel with a biologically active group
DERWENT CLASS: A96; B04; B05; D16
INVENTOR: HERSEL U; RAU H; SCHNEPF R; VETTER D; WEGGE T
PATENT ASSIGNEE: (COMP-N) COMPLEX BIOSYSTEMS GMBH
COUNTRY COUNT: 109

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2006003014	A2	20060112	(200614)*	EN	59[10]	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2006003014	A2	WO 2005-EP7316	20050705

PRIORITY APPLN. INFO: GB 2005-5250 20050315
GB 2004-15041 20040705
EP 2004-19303 20040813

INT. PATENT CLASSIF.:
IPC ORIGINAL: A61K0047-48 [I,A]; A61K0047-48 [I,C]

BASIC ABSTRACT:

WO 2006003014 A2 UPAB: 20060227

NOVELTY - Hydrogel comprising several opening pores comprising reversible prodrug linkers for covalently linking the hydrogel with a biologically active group within the pore, and where such pores are of a size that they are accessible to the biologically active group between the opening and the position, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a polymeric prodrug comprising the hydrogel, biological active group and reversible prodrug linker, where the prodrug linker covalently links to the hydrogel and biological active group, the hydrogel has several pores with openings on the surface, and the diameter of the pores is larger than the biological active group at all points of the pore between one of the openings and the position of the biological active group;

(2) producing a mesoporous hydrogel-biological active group conjugate comprises synthesizing the mesoporous hydrogel; connecting a prodrug linker to the mesoporous hydrogel; and conjugating a biologically active group to the prodrug linker; and (3) release of the biological active group comprises applying the polymeric prodrug; cleavage of the prodrug linkers; and release of the biologically active group.

ACTIVITY - CNS-Gen.; Antimicrobial; Cytostatic; Antibacterial; Fungicide; Virucide; Analgesic; Contraceptive; Antiinflammatory; Cardiovascular-Gen.; Vasotropic.

No biological data given.

MECHANISM OF ACTION - Vaccine; Alpha-1-proteinase Inhibitor; Antitrypsin.

USE - In prodrug in form of medical implant (e.g. bead-shaped form) for delivering biologically active group, e.g. polypeptides consisting of ACTH (Adrenocorticotropic hormone), adenosine deaminase and agalsidase, albumin, antitrypsins, aprotinin and asparaginases (claimed).

ADVANTAGE - The hydrogel provides mesoporous hydrogel prodrugs (MHP), which provides depot formulations without the need for encapsulation. The MHP administered in the form of drug depot, which provides for a sustained release of the biologically active group over a desired period of time.

MANUAL CODE: CPI: A10-E01; A10-E05; A12-V01; A12-V02; B04-C01; B04-C02; B04-C03B; B04-C03C; B04-C03D; B04-E06; B04-E07C; B04-G01; B04-G21; B04-G22; B04-G23; B04-H01; B04-J01; B04-L01; B04-N02; B04-N06; B04-N08; B10-B01B; B10-B02E; B10-B02J; B12-M02G; B12-M10A4; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-F01; B14-F02; B14-H01; B14-J01; B14-P01; B14-S11A; D05-H07; D05-H11; D05-H12D2; D05-H12D8; D05-H17C

TECH

PHARMACEUTICALS - Preferred component: The biologically active group is a biopolymer, organic small molecule bioactive agent, anti-sense or interfering oligonucleotide, or anti-sense or interfering nucleic acid. The biopolymer is selected from proteins or polypeptides consisting of ACTH (Adrenocorticotropic hormone), adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2,3,4,6, 10, 11, 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), TSH, urate oxidase, urokinase, vaccines, or plant proteins such as lectins and ricins (preferably insulin). The organic small molecule bioactive agents consisting of central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting or cardiovascular agents with a primary or secondary amino group. The polymeric prodrug is a cascade prodrug. The prodrug linker comprises a carbamate group. The prodrug linker is attached to a non-biodegradable backbone of the hydrogel. The reversible prodrug linker comprises a masking group and an activating group (preferably carbarnate bond), and have a functional group. The functional group is selected from the functional groups consisting of carboxylic acid or its derivatives, carbonate or its derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid or its derivatives, ketone, amino, aldehyde, thiol and disulfide groups.

Preferred Conjugate: In conjugate, the prodrug linker has two functional groups, a first one of the two functional groups being complementary to a functional group attached to the mesoporous hydrogel and a second one of the two functional groups being conjugable to the biologically active group. The first functional group (a1) is carboxylic acid or its derivatives, amino, maleimide, thiol, sulfonic acid or its derivatives, carbonate or its derivatives, carbamate or its derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid or its derivatives, phosphonic acid or its derivatives, haloacetyl, alkyl halides, acryloyl and other alpha-beta unsaturated michael acceptors, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane or aziridine (preferably thiol or maleimide group). The second functional groups is selected from carboxylic acid or its derivatives, carbonate or its derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid or its derivatives, ketone, amino, aldehyde, thiol or disulfide groups. The biologically active group has a functional

group complimentary to the second one of the two functional groups. The functional group is selected from the functional groups consisting of thiol, carboxylic acid, amino, hydroxyl, ketone or imidazole. The hydrogel is functionalized with a functional group selected (a1). The prodrug linker is attached to a non-degradable backbone of the mesoporous hydrogel.

Preferred Method: The rate of the cleavage in the second step is governed by pH. The cleavage of the prodrug linker occurs substantially chemically or enzymatically. The release of the biologically active group is independent of a degradation of the biodegradable hydrogel. The hydrogel degradates into products having a molecular weight of less than 50 (preferably 30)kDa.

POLYMERS - Preferred Compound: The hydrogel is synthesized from polymers consisting of polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate-based polmers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamide) such as poly(hydroxypropylmethacrylamide) (HMPA), poly(acrylates), poly(methacrylate) like poly(hydroxyethylmethacrylate), poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid) or poly lysine, collagen, and **gelatin**, copolymers, grafted copolymers, cross-linked polymers, or their block copolymers (preferably polyacrylamide or its derivate; especially poly(ethylene glycol acrylamide) or its derivate). The hydrogel or cross-linkers of the hydrogel/mesoporous hydrogel further comprises biodegradable bonds selected from chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds (preferably enzymatically cleavable).

PHARMACEUTICALS - Preferred component: The biologically active group is a biopolymer, organic small molecule bioactive agent, anti-sense or interfering oligonucleotide, or anti-sense or interfering nucleic acid. The biopolymer is selected from proteins or polypeptides consisting of ACTH (Adrenocorticotropic hormone), adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG)., hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2,3,4,6, 10, 11, 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator

(tPA), TSH, urate oxidase, urokinase, vaccines, or plant proteins such as lectins and ricins (preferably insulin). The organic small molecule bioactive agents consisting of central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting or cardiovascular agents with a primary or secondary amino group. The polymeric prodrug is a cascade prodrug. The prodrug linker comprises a carbamate group. The prodrug linker is attached to a non-biodegradable backbone of the hydrogel. The reversible prodrug linker comprises a masking group and an activating group (preferably carbarnate bond), and have a functional group. The functional group is selected from the functional groups consisting of carboxylic acid or its derivatives, carbonate or its derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid or its derivatives, ketone, amino, aldehyde, thiol and disulfide groups.

Preferred Conjugate: In conjugate, the prodrug linker has two functional groups, a first one of the two functional groups being complementary to a functional group attached to the mesoporous hydrogel and a second one of the two functional groups being conjugable to the biologically active group. The first functional group (a1) is carboxylic acid or its derivatives, amino, maleimide, thiol, sulfonic acid or its derivatives, carbonate or its derivatives, carbamate or its derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid or its derivatives, phosphonic acid or its derivatives, haloacetyl, alkyl halides, acryloyl and other alpha-beta unsaturated michael acceptors, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane or aziridine (preferably thiol or maleimide group). The second functional groups is selected from carboxylic acid or its derivatives, carbonate or its derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid or its derivatives, ketone, amino, aldehyde, thiol or disulfide groups. The biologically active group has a functional group complimentary to the second one of the two functional groups. The functional group is selected from the functional groups consisting of thiol, carboxylic acid, amino, hydroxyl, ketone or imidazole. The hydrogel is functionalized with a functional group selected (a1). The prodrug linker is attached to a non-degradable backbone of the mesoporous hydrogel.

Preferred Method: The rate of the cleavage in the second step is governed by pH. The cleavage of the prodrug linker occurs substantially chemically or enzymatically. The release of the biologically active group is independent of a degradation of the biodegradable hydrogel. The hydrogel degradates into products having a molecular weight of less than 50 (preferably 30)kDa.

POLYMERS - Preferred Compound: The hydrogel is synthesized from polymers consisting of polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate-based polmers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamide) such as poly(hydroxypropylmethacrylamide) (HMPA), poly(acrylates), poly(methacrylate) like poly(hydroxyethylmethacrylate), poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid) or poly lysine, collagen, and gelatin, copolymers, grafted copolymers, cross-linked polymers, or their block copolymers (preferably polyacrylamide or its derivate; especially poly(ethylene glycol acrylamide) or its derivate). The hydrogel or

cross-linkers of the hydrogel/mesoporous hydrogel further comprises biodegradable bonds selected from chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds (preferably enzymatically cleavable).

IT UPIT 20060227
86594-CL 86594-PRD 86594-USE; 87030-CL 87030-PRD 87030-USE; 108947-CL 108947-PRD 108947-USE; 86886-CL 86886-PRD 86886-USE; 111065-CL 111065-PRD 111065-USE; 87487-CL 87487-PRD 87487-USE; 87569-CL 87569-PRD 87569-USE; 87628-CL 87628-PRD 87628-USE; 88873-CL 88873-PRD 88873-USE; 274369-CL 274369-PRD 274369-USE; 89804-CL 89804-PRD 89804-USE; 92701-CL 92701-PRD 92701-USE; 111470-CL 111470-PRD 111470-USE; 94444-CL 94444-PRD 94444-USE; 91375-CL 91375-PRD 91375-USE; 95143-CL 95143-PRD 95143-USE; 91489-CL 91489-PRD 91489-USE; 96184-CL 96184-PRD 96184-USE; 96206-CL 96206-PRD 96206-USE; 114126-CL 114126-PRD 114126-USE; 96948-CL 96948-PRD 96948-USE; 97927-CL 97927-PRD 97927-USE; 97929-CL 97929-PRD 97929-USE; 97946-CL 97946-PRD 97946-USE; 97951-CL 97951-PRD 97951-USE; 97954-CL 97954-PRD 97954-USE; 97959-CL 97959-PRD 97959-USE; 97940-CL 97940-PRD 97940-USE; 114367-CL 114367-PRD 114367-USE; 97942-CL 97942-PRD 97942-USE; 97865-CL 97865-PRD 97865-USE; 97868-CL 97868-PRD 97868-USE; 97869-CL 97869-PRD 97869-USE; 115052-CL 115052-PRD 115052-USE; 97905-CL 97905-PRD 97905-USE; 157619-CL 157619-PRD 157619-USE; 97915-CL 97915-PRD 97915-USE; 111550-CL 111550-PRD 111550-USE; 202589-CL 202589-PRD 202589-USE; 99316-CL 99316-PRD 99316-USE; 105703-CL 105703-PRD 105703-USE; 103220-CL 103220-PRD 103220-USE; 104225-CL 104225-PRD 104225-USE; 103599-CL 103599-PRD 103599-USE; 104749-CL 104749-PRD 104749-USE; 104886-CL 104886-PRD 104886-USE; 102650-CL 102650-PRD 102650-USE; 133911-CL 133911-PRD 133911-USE; 153799-CL 153799-PRD 153799-USE; 203579-CL 203579-PRD 203579-USE; 107421-CL 107421-PRD 107421-USE; 107856-CL 107856-PRD 107856-USE; 107958-CL 107958-PRD 107958-USE; 108861-CL 108861-PRD 108861-USE; 108875-CL 108875-PRD 108875-USE; 109601-CL 109601-PRD 109601-USE; 203311-CL 203311-PRD 203311-USE; 109929-CL 109929-PRD 109929-USE; 109946-CL 109946-PRD 109946-USE; 97834-CL 97834-PRD 97834-USE; **99369-CL 99369-PRD 99369-USE**; 104376-CL 104376-PRD 104376-USE; 104411-CL 104411-PRD 104411-USE; 900-CL 900-PRD 900-USE; 104472-CL 104472-PRD 104472-USE; 92818-CL 92818-PRD 92818-USE; 104328-CL 104328-PRD 104328-USE; 97115-CL 97115-PRD 97115-USE; 86923-CL 86923-PRD 86923-USE; 110651-CL 110651-PRD 110651-USE; 100074-CL 100074-PRD 100074-USE; 90114-CL 90114-PRD 90114-USE; 86730-CL 86730-PRD 86730-USE; 90356-CL 90356-PRD 90356-USE; 107779-CL 107779-PRD 107779-USE; 96860-CL 96860-PRD 96860-USE; 95972-CL 95972-PRD 95972-USE; 104492-CL 104492-PRD 104492-USE; 104486-CL 104486-PRD 104486-USE; 104380-CL 104380-PRD 104380-USE; 104379-CL 104379-PRD 104379-USE; 104369-CL 104369-PRD 104369-USE; 104421-CL 104421-PRD 104421-USE; 1062-CL 1062-PRD 1062-USE; 104427-CL 104427-PRD 104427-USE; 104413-CL 104413-PRD 104413-USE; 91481-CL 91481-PRD 91481-USE

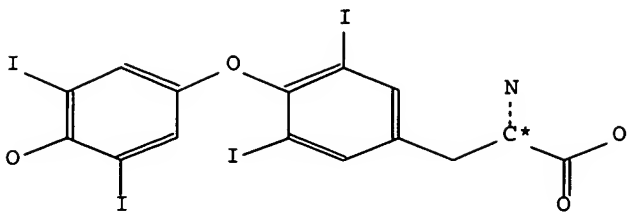
M1 *61* A111 A960 C710 G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M411 M423 M431 M510 M520 M532 M540 M630 M720 M782 N152 P210 P220 P241 P411 P420 P434 P446 P520 P522 P527 P528 P616 P841 P842 P843 R052 M905 M904
DCN: **RA11AM-K RA11AM-M RA11AM-P**
DCR: **99369-K 99369-M 99369-P**

AN.S DCR-99369
CN.P LEVOTHYROXINE SODIUM
CN.S 2-amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionate; Sodium
SDCN RA11AM

CM 1

Na

CM 2



L86 ANSWER 12 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-087378 [09] WPIX
CROSS REFERENCE: 2006-136071
DOC. NO. CPI: C2006-031601 [09]
TITLE: Polymeric prodrug, useful for sustained release of bioactive agents, comprises a hydrogel, a biologically active moiety and a reversible prodrug linker
DERWENT CLASS: A18; A28; A96; B05; D16; D22
INVENTOR: HERSEL U; RAU H; SCHNEPF R; VETTER D; WEGGE T
PATENT ASSIGNEE: (HERS-I) HERSEL U; (RAUH-I) RAU H; (SCHN-I) SCHNEPF R; (VETT-I) VETTER D; (WEGG-I) WEGGE T; (COMP-N) COMPLEX BIOSYSTEMS GMBH
COUNTRY COUNT: 34

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20060002890	A1	20060105	(200609)*	EN	35	[10]
EP 1625856	A1	20060215	(200613)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20060002890	A1	US 2004-960851	20041007
EP 1625856	A1	EP 2004-19303	20040813

PRIORITY APPLN. INFO: EP 2004-19303 20040813
GB 2004-15041 20040705
INT. PATENT CLASSIF.:
IPC ORIGINAL: A61K0031-74 [I,C]; A61K0031-785 [I,A]; A61K0031-795 [I,A] ; A61K0047-48 [I,A]; A61K0047-48 [I,C]
BASIC ABSTRACT:
US 20060002890 A1 UPAB: 20060206
NOVELTY - Polymeric prodrug (A) comprises a hydrogel (1), a biologically active moiety (2) and a reversible prodrug linker (3), where (3) covalently links (1) and (2) at a position; and (1) has a plurality of pores with openings on the surface of (1) and the diameter of the pores is larger than

(2) at least at all points of the pore between at least one of the openings and the position of (2).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a hydrogel (1) having a plurality of pores with openings, where the pores comprising (3) for covalently linking (1) with (2) at a position within the pore, where such pores are of such a size that they are accessible to (2) between the opening and the position; (2) a method for the manufacture of a mesoporous hydrogel-biologically active moiety conjugate, comprising: synthesizing the mesoporous hydrogel; followed by connecting a prodrug linker to the mesoporous hydrogel; and conjugating (2) to (3), where the connecting and conjugating can be carried out in either order; and (3) a method of treatment comprising: (a) applying (A); (b) cleaving (3); and (c) releasing (2).

USE - (A) is useful for sustained release of (2).

ADVANTAGE - (A) provides sustained release of (2) over desired period of time and does not need encapsulation. The pharmacokinetics of (A) to release (2) (insulin) was assessed in vitro. The results showed that the amount of insulin released was 13.5 nmol at a half life (t1/2) of 168 hours.

MANUAL CODE: CPI: A10-E01; A12-V01; B04-B04D2; B04-C01; B04-C02; B04-C03; B04-F10; B04-F11; B04-G01; B04-G21; B04-G22; B04-H01; B04-H02; B04-H04; B04-H05; B04-H06; B04-H07; B04-H08; B04-H19; B04-J01; B04-J03; B04-J04; B04-J05; B04-J10; B04-J11; B04-L02; B04-L03; B04-L05; B04-M01; B04-N01; B04-N02; B04-N04; B04-N06; B04-N08; B10-B02E; B12-M10A; D09-C

TECH

PHARMACEUTICALS - Preferred Components: (2) comprises a biopolymer and is proteins or polypeptides consisting of ACTH, adenosine deaminase, agalsidase, albumin, alpha-1 antitrypsin (AAT), alpha-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, deoxyribonuclease (DNase), endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2, 3, 4, 6, 10, 11, 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a or gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, platelet derived growth factor (PDGF), pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatotropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), thyroid stimulating hormone (TSH), urate oxidase, urokinase, vaccines or plant proteins, preferably comprises insulin. (2) comprises an organic small molecule bioactive agent (central nervous system-active agents, anti-infective agents, antineoplastic agents, antibacterial agents, anti-fungal agents, analgesic agents, contraceptive agents, anti-inflammatory agents, steroidal agents, vasodilating agents, vasoconstricting agents or cardiovascular agents) or an anti-sense or interfering oligonucleotide.

(A) comprises a cascade prodrug or a carbamate group. Preferred Composition: (A) is in the form of a medical implant in a substantially bead-shaped form. Preferred Method: The rate of the cleavage is governed by pH. The cleavage of (3) occurs substantially chemically or enzymatically. The release of (2) is independent of a degradation of (1). (1) degrades into products having a molecular weight of less than 50 (preferably less than 30) kDa.
POLYMERS - Preferred Components: (1) is synthesized from polyalkyloxy-based polymers, dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES), carbohydrate-based polymers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly-(acrylamides), poly(acrylates), poly(methacrylates), poly-(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters), poly(lactic acid), poly(glycolic acids), poly(iminocarbonates), poly(amino acids), poly(glutamic acid), polylysine, collagen, and **gelatin**, and copolymers, grafted copolymers, cross-linked polymers, and block copolymers. (1) polyacrylamide or poly(ethylene glycol acrylamide) or its derivative. (1) further comprises biodegradable bonds (chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds) that are enzymatically cleavable. (3) is attached to a non-biodegradable backbone of (1). The crosslinkers of (1) further comprises biodegradable bonds (chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds). (3) comprises a masking group and an activating group and a carbamate bond. (3) has a functional group (carboxylic acid and derivatives, carbonate and derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid and derivatives, ketone, amino, aldehyde, thiol or disulfide groups) and are attached to a non-biodegradable backbone of (1). In the method of manufacturing the mesoporous hydrogel-biologically active moiety conjugate, (3) has two functional groups, where a first one of the two functional groups being complementary to a functional group attached to the mesoporous hydrogel and a second one of the two functional groups being conjugable to (2). The first one of the two functional groups is carboxylic acid and activated derivatives, amino, maleimide, thiol, sulfonic acid and derivatives, carbonate and derivatives, carbamate and derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, alpha-beta unsaturated Michael acceptors, arylating agents, aryl fluorides, hydroxylamine, disulfides, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane, or aziridine; preferably thiol or maleimide. The second one of the two functional groups is carboxylic acid and derivatives, carbonate and derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid and derivatives, ketone, amino, aldehyde, thiol and disulfide groups. (2) has a moiety functional group (thiol, carboxylic acid, amino, hydroxyl, ketone or imidazole) complimentary to the second one of the two functional groups. (1) is functionalized with functional groups of (3), preferably functionalized with maleimide. (3) is attached to a non-degradable backbone of the mesoporous hydrogel.
PHARMACEUTICALS - Preferred Components: (2) comprises a biopolymer and is proteins or polypeptides consisting of ACTH, adenosine deaminase, agalsidase, albumin, alpha-1 antitrypsin (AAT), alpha-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, deoxyribonuclease (DNase), endorphins, enfuvirtide, enkephalins,

erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2, 3, 4, 6, 10, 11, 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a or gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, platelet derived growth factor (PDGF), pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatotropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), thyroid stimulating hormone (TSH), urate oxidase, urokinase, vaccines or plant proteins, preferably comprises insulin. (2) comprises an organic small molecule bioactive agent (central nervous system-active agents, anti-infective agents, antineoplastic agents, antibacterial agents, anti-fungal agents, analgesic agents, contraceptive agents, anti-inflammatory agents, steroidal agents, vasodilating agents, vasoconstricting agents or cardiovascular agents) or an anti-sense or interfering oligonucleotide. (A) comprises a cascade prodrug or a carbamate group. Preferred Composition: (A) is in the form of a medical implant in a substantially bead-shaped form. Preferred Method: The rate of the cleavage is governed by pH. The cleavage of (3) occurs substantially chemically or enzymatically. The release of (2) is independent of a degradation of (1). (1) degrades into products having a molecular weight of less than 50 (preferably less than 30) kDa.

POLYMERS - Preferred Components: (1) is synthesized from polyalkyloxy-based polymers, dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES), carbohydrate-based polymers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly-(acrylamides), poly(acrylates), poly(methacrylates), poly-(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters), poly(lactic acid), poly(glycolic acids), poly(iminocarbonates), poly(amino acids), poly(glutamic acid), polylysine, collagen, and **gelatin**, and copolymers, grafted copolymers, cross-linked polymers, and block copolymers. (1) polyacrylamide or poly(ethylene glycol acrylamide) or its derivative. (1) further comprises biodegradable bonds (chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds) that are enzymatically cleavable. (3) is attached to a non-biodegradable backbone of (1). The crosslinkers of (1) further comprises biodegradable bonds (chemically-cleavable bonds consisting of phosphate, phosphonate, carbonate, carbamate, disulfide or ester bonds). (3) comprises a masking group and an activating group and a carbamate bond. (3) has a functional group (carboxylic acid and derivatives, carbonate and derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid and derivatives, ketone, amino, aldehyde, thiol or disulfide groups) and are attached to a non-biodegradable backbone of (1). In the method of manufacturing the mesoporous hydrogel-biologically active moiety conjugate, (3) has two functional groups, where a first one of the two functional groups being complementary to a functional group attached to

the mesoporous hydrogel and a second one of the two functional groups being conjugable to (2). The first one of the two functional groups is carboxylic acid and activated derivatives, amino, maleimide, thiol, sulfonic acid and derivatives, carbonate and derivatives, carbamate and derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, alpha-beta unsaturated Michael acceptors, arylating agents, aryl fluorides, hydroxylamine, disulfides, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane, or aziridine; preferably thiol or maleimide. The second one of the two functional groups is carboxylic acid and derivatives, carbonate and derivatives, hydroxyl, hydrazine, hydroxylamine, maleamic acid and derivatives, ketone, amino, aldehyde, thiol and disulfide groups. (2) has a moiety functional group (thiol, carboxylic acid, amino, hydroxyl, ketone or imidazole) complimentary to the second one of the two functional groups. (1) is functionalized with functional groups of (3), preferably functionalized with maleimide. (3) is attached to a non-degradable backbone of the mesoporous hydrogel.

IT UPIT 20060206
97115-CL 97115-USE; 104328-CL 104328-USE; 92818-CL 92818-USE; 86923-CL 86923-USE; 110651-CL 110651-USE; 100074-CL 100074-USE; 184613-CL 184613-USE; 90114-CL 90114-USE; 104380-CL 104380-USE; 104486-CL 104486-USE; 104492-CL 104492-USE; 104379-CL 104379-USE; 1062-CL 1062-USE; 104376-CL 104376-USE; 91640-CL 91640-USE; 86594-CL 86594-USE; 86886-CL 86886-USE; 690047-CL 690047-USE; 111065-CL 111065-USE; 87487-CL 87487-USE; 184587-CL 184587-USE; 87569-CL 87569-USE; 135600-CL 135600-USE; 87628-CL 87628-USE; 87853-CL 87853-USE; 88873-CL 88873-USE; 274369-CL 274369-USE; 89818-CL 89818-USE; 97834-CL 97834-USE; 92701-CL 92701-USE; 91483-CL 91483-USE; 94144-CL 94144-USE; 111470-CL 111470-USE; 94189-CL 94189-USE; 94444-CL 94444-USE; 114092-CL 114092-USE; 91375-CL 91375-USE; 274041-CL 274041-USE; 91373-CL 91373-USE; 95143-CL 95143-USE; 184616-CL 184616-USE; 95649-CL 95649-USE; 91489-CL 91489-USE; 426064-CL 426064-USE; 96184-CL 96184-USE; 96206-CL 96206-USE; 114126-CL 114126-USE; 90882-CL 90882-USE; 96786-CL 96786-USE; 200757-CL 200757-USE; 96948-CL 96948-USE; 111149-CL 111149-USE; 184598-CL 184598-USE; 97927-CL 97927-USE; 97929-CL 97929-USE; 97946-CL 97946-USE; 97951-CL 97951-USE; 97954-CL 97954-USE; 97959-CL 97959-USE; 97940-CL 97940-USE; 114367-CL 114367-USE; 97942-CL 97942-USE; 626652-CL 626652-USE; 97865-CL 97865-USE; 97867-CL 97867-USE; 97869-CL 97869-USE; 115052-CL 115052-USE; 97905-CL 97905-USE; 157619-CL 157619-USE; 97915-CL 97915-USE; 111550-CL 111550-USE; 202589-CL 202589-USE; 108947-CL 108947-USE; 99316-CL 99316-USE; 89180-CL 89180-USE; 105703-CL 105703-USE; 103220-CL 103220-USE; 1021345-CL 1021345-USE; 104225-CL 104225-USE; 103599-CL 103599-USE; 172493-CL 172493-USE; 104749-CL 104749-USE; 104886-CL 104886-USE; 102650-CL 102650-USE; 133911-CL 133911-USE; 153799-CL 153799-USE; 203579-CL 203579-USE; 107436-CL 107436-USE; 107421-CL 107421-USE; 107856-CL 107856-USE; 107958-CL 107958-USE; 108831-CL 108831-USE; 108861-CL 108861-USE; 108875-CL 108875-USE; 109601-CL 109601-USE; 203311-CL 203311-USE; 109929-CL 109929-USE; 109946-CL 109946-USE; **99369-CL 99369-USE**

M2 *99* A111 A960 C710 G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M411 M424 M430 M510 M520 M532 M540 M630 M740 M782 N103 R052 M905 M904

DCN: **RA11AM-K RA11AM-M**

DCR: **99369-K 99369-M**

AN.S DCR-99369

CN.P LEVOTHYROXINE SODIUM

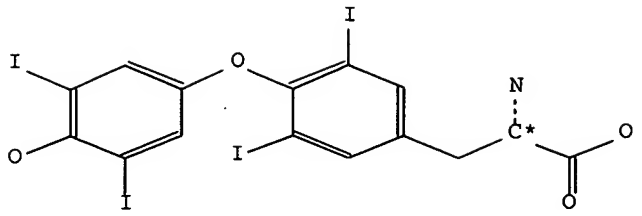
CN.S 2-amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionate; Sodium

SDCN RA11AM

CM 1

Na

CM 2



L86 ANSWER 13 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2007-036301 [05] WPIX
DOC. NO. CPI: C2007-013844 [05]
TITLE: Polymeric prodrug, useful to alter or to eliminate undesirable properties in the parent molecule, comprises polymer attached via a permanent bond to a bicine linker
DERWENT CLASS: A11; A14; A28; A96; B05; B07
INVENTOR: HERSEL U; RAU H; VETTER D; WEGGE T
PATENT ASSIGNEE: (COMP-N) COMPLEX BIOSYSTEMS GMBH
COUNTRY COUNT: 113

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
GB 2427360	A	20061227	(200705)*	EN	65	[10]
WO 2006136586	A2	20061228	(200705)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2427360	A	GB 2005-12705	20050622
WO 2006136586	A2	WO 2006-EP63418	20060621

PRIORITY APPLN. INFO: GB 2005-12705 20050622
INT. PATENT CLASSIF.:
IPC ORIGINAL: A61K0038-16 [I,A]; A61K0047-48 [I,A]; C07K0017-00 [I,C]; C07K0017-06 [I,A]; C07K0017-08 [I,A]; C08G0063-00 [I,C]; C08G0063-91 [I,A]

BASIC ABSTRACT:
GB 2427360 A UPAB: 20070119
NOVELTY - Polymeric prodrug (A) comprises at least one polymer attached via at least one permanent bond to a bicine linker, which is attached via a temporary linkage to an amine containing biologically active moiety.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) the 5 preparations of (A); (2) a method of hydrolyzing (A) comprising placing (A) in solution with a pH of approximately 7.4;
(3) a method of administration of an amine-containing moiety to a living organism comprising providing (A), administering (A) to the living organism, and cleaving the amine-containing moiety from (A) by non-enzymatic reaction; and
(4) a method of providing a useful concentration of a biologically active molecule by in vivo cleavage of the biologically active molecule from (A).
USE - (A) is useful in a transient manner to alter or to eliminate undesirable properties in the parent molecule.
ADVANTAGE - (A) has no side effects and avoids the risk of overdosing.

MANUAL CODE: CPI: A10-E01; A12-V01; A12-W11L; B02-A; B02-D; B02-F; B02-I; B02-K; B02-S; B04-B03C; B04-C01; B04-C02; B04-E10; B04-G01; B04-G21; B04-G22; B04-G23; B04-H01; B04-K01; B04-L01; B04-N02; B04-N04; B04-N06; B06-H; B07-H; B08-D02; B09-D01; B10-A08; B10-A10; B10-B01B; B10-B02E; B10-B03B; B12-M10A5; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-F01; B14-F02; B14-H01; B14-J01; B14-J02; B14-P01; B14-S15

TECH

BIOLOGY - Preferred Components: The biologically active moiety is biologically moieties consisting of small molecule biologically active agents or biopolymers. The biopolymers are biopolymers consisting of proteins, polypeptides, oligonucleotides and peptide nucleic acids. The polypeptides are polypeptides consisting of adrenocorticotropic hormone, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin, alfa-1 proteinase inhibitor, alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (sahnon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides (GLP-1), glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein, gonadotropin chorionic, hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idumonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2,3,4,6,10,11,12), IL-1 receptor antagonist, insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor, transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, platelet-derived growth factor, pepsin, platelet activating factor acetylhydrolase, prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator, thyroid stimulating hormone, urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is: a protein prepared by recombinant DNA technology; and the group of proteins consisting of antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins, antibodies, calcitonin, G-CSF, GM-CSF, erythropoietins, hemoglobins, interleukins, insulins, interferons, SOD, somatropin, TNF, TNF-receptor-IgC Fc and GLP-1. The small molecule biologically active agents are central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating,

vasoconstricting, cardiovascular agents with at least one primary or secondary amino group, and compounds of daunorubicin, doxorubicin, idarubicm, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxaxin, enoxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamin, dobutamin, lisinopril, serotonin, acivicin and carbutamid.

ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (A) comprises: e.g. providing a starting molecule (I) of formula (A-C(R4)(R7)-C(=O)-D-solid phase), displacing A with a starting molecule (II) of formula ((R2-O-C(X-PG)(R8)-C(R5)(R6))NH(C(R9)(R10)-C(R11)(R12)-O-R3)), cleaving the resulting intermediate from the solid phase and cleaving all present protecting groups to form an intermediate (III) of formula ((R2-O-C(X)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R7)-C(=O)-D), and attaching an polymer R1 to X in the (III) to form (A); and providing starting molecule (IV) of formula (H2N-C(R4)(X-PG)-C(=O)-D-solid phase), forming an intermediate (V) of formula ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X-PG)-C(=O)-D-solid phase) by at least one substitution or reductive alkylation, cleaving (V) from the solid phase and cleaving all present protecting groups to form an intermediate (VI) of formula ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X)-C(=O)-D), and attaching an polymer R1 to X in the (III) to form (A).

Preferred Process: The cleaving of the amine-containing moiety from the carrier by a non-enzymatic reaction of the nucleophile-containing linker and is carried out in an extra-cellular fluid. The non-enzymatic reaction comprises a step of hydrolysis and is carried out at a pH of approximately 7.4.

Preferred Components: The polymeric prodrug linker reagent having alkylamino compound of formulae ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X-R1)-C(=O)-T), ((R2-O-C(R7)(R8)-C(R1-X)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R5)-C(=O)-T) and ((R2-O-C(R1-X)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R7)-C(=O)-T).

T = D or A;

D = amine containing biologically active moiety;

A = leaving group (preferably of chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy, N-hydroxysulfosuccinimidyl or heteroaryl); either

R1 = polymer (preferably polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate based polmers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamides) such as poly(hydroxypropylmethacrylamide) (HMPA), polyacrylates), poly(methacrylates) like poly(hydroxyethylmethacrylate), poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid), collagen, **gelatin**, copolymers, grafted copolymers, cross-linked polymers, and block copolymers, hydrogel, branched or hyperbranched polymer, a dendrimer or dense star polymer, biopolymer or protein), biologically active substances or functional group (preferably thiol, maleimide, amino, carboxylic acid and derivatives, carbonate and derivatives, carbamate and derivatives, aldehyde, and haloacetyl) for linkage to X; and

X = R13-Y1; or

XR1 = S-succinimido, amide, carbamate, thioether and urea;

Y1 = O, S, NR6, succinimide, maleimide, unsaturated C-C bonds or heteroatom containing free electron pair or is absent;
R13 = cyclical alkyl, heteroalkyl or (hetero)aryls (all optionally substituted);
R2, R3 = H, acyl or OH; and
R4-R12 = cyclical alkyl, heteroalkyl, (hetero)aryls (all optionally substituted), CN, NO2, halo, COO, carboxamide, H or X-R1.
BIOLOGY - Preferred Components: The biologically active moiety is biologically moieties consisting of small molecule biologically active agents or biopolymers. The biopolymers are biopolymers consisting of proteins, polypeptides, oligonucleotides and peptide nucleic acids. The polypeptides are polypeptides consisting of adrenocorticotropic hormone, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin, alfa-1 proteinase inhibitor, alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (sahnon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides (GLP-1), glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein, gonadotropin chorionic, hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idumonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2,3,4,6,10,11,12), IL-1 receptor antagonist, insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta la, beta lb, gamma la, gamma lb), keratinocyte growth factor, transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, platelet-derived growth factor, pepsin, platelet activating factor acetylhydrolase, prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator, thyroid stimulating hormone, urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is: a protein prepared by recombinant DNA technology; and the group of proteins consisting of antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins, antibodies, calcitonin, G-CSF, GM-CSF, erythropoietins, hemoglobins, interleukins, insulins, interferons, SOD, somatropin, TNF, TNF-receptor-IgC Fc and GLP-1. The small molecule biologically active agents are central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, cardiovascular agents with at least one primary or secondary amino group, and compounds of daunorubicin, doxorubicin, idarubicm, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxaxin, enoxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamin, dobutamin, lisinopril, serotonin, acivicin and carbutamid.
ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (A) comprises: e.g. providing a starting molecule (I) of formula (A-C(R4)(R7)-C(=O)-D-solid phase), displacing A with a starting molecule (II) of formula ((R2-O-C(X-PG)(R8)-C(R5)(R6))NH(C(R9)(R10)-C(R11)(R12)-O-R3)), cleaving the resulting intermediate from the solid phase and cleaving all present protecting groups to form an intermediate (III) of formula ((R2-O-C(X)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R7)-C(=O)-

D), and attaching an polymer R1 to X in the (III) to form (A); and providing starting molecule (IV) of formula (H2N-C(R4)(X-PG)-C(=O)-D-solid phase), forming an intermediate (V) of formula ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X-PG)-C(=O)-D-solid phase) by at least one substitution or reductive alkylation, cleaving (V) from the solid phase and cleaving all present protecting groups to form an intermediate (VI) of formula ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X)-C(=O)-D), and attaching an polymer R1 to X in the (III) to form (A).

Preferred Process: The cleaving of the amine-containing moiety from the carrier by a non-enzymatic reaction of the nucleophile-containing linker and is carried out in an extra-cellular fluid. The non-enzymatic reaction comprises a step of hydrolysis and is carried out at a pH of approximately 7.4.

Preferred Components: The polymeric prodrug linker reagent having alkylamino compound of formulae ((R2-O-C(R7)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(X-R1)-C(=O)-T), ((R2-O-C(R7)(R8)-C(R1-X)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R5)-C(=O)-T) and ((R2-O-C(R1-X)(R8)-C(R5)(R6))N(C(R9)(R10)-C(R11)(R12)-O-R3)-C(R4)(R7)-C(=O)-T).

T = D or A;

D = amine containing biologically active moiety;

A = leaving group (preferably of chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy, N-hydroxysulfosuccinimidyl or heteroaryl); either

R1 = polymer (preferably polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate based polmers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamides) such as poly(hydroxypropylmethacrylamide) (HMPA), polyacrylates), poly(methacrylates) like poly(hydroxyethylmethacrylate), poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid), collagen, **gelatin**, copolymers, grafted copolymers, cross-linked polymers, and block copolymers, hydrogel, branched or hyperbranched polymer, a dendrimer or dense star polymer, biopolymer or protein), biologically active substances or functional group (preferably thiol, maleimide, amino, carboxylic acid and derivatives, carbonate and derivatives, carbamate and derivatives, aldehyde, and haloacetyl) for linkage to X; and

X = R13-Y1; or

XR1 = S-succinimido, amide, carbamate, thioether and urea;

Y1 = O, S, NR6, succinimide, maleimide, unsaturated C-C bonds or heteroatom containing free electron pair or is absent;

R13 = cyclical alkyl, heteroalkyl or (hetero)aryls (all optionally substituted);

R2, R3 = H, acyl or OH; and

R4-R12 = cyclical alkyl, heteroalkyl, (hetero)aryls (all optionally substituted), CN, NO2, halo, COO, carboxamide, H or X-R1.

IT UPIT 20070119

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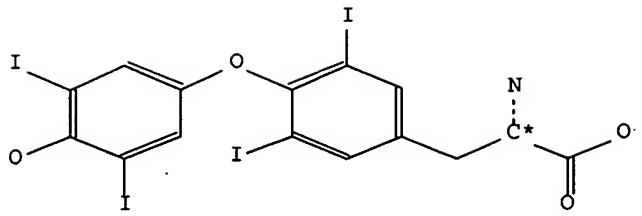
RA11AM-Q
DCR: **99369-K 99369-M 99369-P**
99369-Q

AN.S DCR-99369
CN.P LEVOTHYROXINE SODIUM
CN.S 2-amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionat
e; Sodium
SDCN RA11AM

CM 1

Na

CM 2



L86 ANSWER 14 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2007-059188 [07] WPIX
DOC. NO. CPI: C2007-021957 [07]
DOC. NO. NON-CPI: N2007-041283 [07]
TITLE: Preparation, useful to support administration and/or to enhance pharmaceutical active substance in human or animal body, comprises a polar carrier substance and a broad band resonator
DERWENT CLASS: A96; B05; B07; D13; D21; P33
INVENTOR: NATTERER S
PATENT ASSIGNEE: (NATT-I) NATTERER S
COUNTRY COUNT: 36

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1728519	A2	20061206	(200707)*	DE	27[2]	
DE 102005025156	A1	20061207	(200707)	DE		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1728519	A2	EP 2006-114870	20060601
DE 102005025156	A1	DE 2005-102005025156	20050601

PRIORITY APPLN. INFO: DE 2005-102005025156 20050601
INT. PATENT CLASSIF.:
IPC ORIGINAL: A61H0039-00 [I,A]; A61K0041-00 [I,A]; A61K0047-00 [I,A]
BASIC ABSTRACT:
EP 1728519 A2 UPAB: 20070129
NOVELTY - Preparation (I) to support administration and/or to enhance active substance, particularly pharmaceutical active substance or nutritional supplement in human or animal body, preferably under avoidance of side-effect, comprises at least a polar carrier substance and at least a broad band resonator.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) a method for the avoidance of toxic effects and/or improvement of consistency of the active substances, which affect the human or animal body by administration comprising at least one broadband resonator; and (2) multi-level preparations (II) for executing a multi-level therapy, exhibiting different concentrations of the

active substance or resonators and/or different polarity/resonator concentration ratio and/or different polarities.
ACTIVITY - Antirheumatic; Hepatotropic.
MECHANISM OF ACTION - None given.
USE - (I) is useful in the preparation of a substance, preferably medicament to support the administration and/or increases the effect of active agent, preferably pharmaceutical active agent or nutritional supplement; and/or to reduce or avoid injurious effects on the human or animal body of exposure materials, like cosmetic. (I) is useful as bath additives. (I) is useful to treat rheumatism, where the active substance are Bryonia, Rhus toxicodendron, Thuja, Carduus marianus, Cheledonium, Nux vomica, Spirae ulmaria, Dulcamara, Clematis, Veratrum album, Sulfur, or Staphisagria, which are present preferably in the preparation in the concentration from the tincture to D12, preferably in connection with resonator concentration of D1-D12; liver disease, where the active substance are Chelidonium, Carduus marianus, Madragora officinarium and/or Leptandara in a concentration of tincture to D12, preferably in connection with resonator concentration of D1-D15, preferably D2-D4; wound treatment, where the ingredients comprises himalaja salt/rock salt as a resonator, preferably in the concentration of D8, trace element-solution in the concentration of D3-D4, vitamin A and/or B and C, pantothenic acid, an emulsion as oil-in-water emulsion and/or water-in-oil emulsion and grape fruit extract. (I) is useful in diagnosing by information- and/or energetizing- and/or oscillation method (all claimed).
ADVANTAGE - (I) avoids side effect (claimed). (I) provides good absorption compatibility.
MANUAL CODE: CPI: A12-V; A12-V01; B03-F; B05-A01A; B05-A01B; B05-A03; B05-B02A3; B05-B02C; B05-C05; B07-D12; B10-C02; B11-C08; B12-K04; B14-C06; B14-N12; B14-N17B; D03-H01T; D08-B09A

TECH

INORGANIC CHEMISTRY - Preferred Components: The broadband resonator comprises one or more components such as minerals, trace elements, emulsifying agents, gelling agent, essential/non-essential metals/metal salts and/or nonmetals (preferably quartz sand), stone flour, mineral flour, natural salts (preferably sea salt), rock salt or himalaja salt, shell limestone, healing earth, silicon compound, methyl cellulose, alginate, agar-agar, carob seed grain flour, guar flour, silicic acid, iron, zinc, copper, manganese, chrome, molybdenum, vanadium, nickel, tin, silver, gold, iodine, arsenic, silicon, calcium, magnesium, potassium, sodium or germanium, preferably iron and/or iron compound. (I) comprises minimum 5, preferably 15 different components (preferably of mineral components, heavy metal and/or its compounds). (I) comprises at least an schuessler salt and/or at least fluorescence stream.
INSTRUMENTATION AND TESTING - Preferred Components: The broadband resonator comprises plus- and minus-resonator. The concentration of the broadband resonator in a dilution of homeopathic potency is D3-D23, preferably D12-D23. The concentration of the carrier substance or the broadband resonator is adjusted to a ratio of high polarity. The concentration ratio of active substance or active substance of the broadband resonator is greater than 5:1, preferably 1000000:1. The pH of (I) is 8-12.5, preferably 9-10.5; or 5.5, preferably 2-3.5. Preferred Process: (I) is carried out by homeopathic process after administering dimethyl amino azo benzene (DAB), preferably exponential process, particularly in low, middle or higher decimal power or centesimal power, preferably homeopathic chemical dispensary process. (I) is produced by information, energitizing, oscillation, bioresonance, radionic and/or magnetizing method. The broad band resonator used for organ preparation is a multiresonator or an organic resonator. The broadband resonator and/or the active substance are brought into contact to avoid interaction with liposome. The first step exhibits a low concentration or the resonator and/or a high polarity/resonator concentration ratio and further exhibits

high concentration or resonator and/or lower polarity/resonator concentrations ratios and/or low polarities. The interaction between specific active substance and/or the resonator and/or the energetic ratio forms the tissues and structures. The resonator concentration conforms the active agent concentration, preferably in over decimal powers or under the active substance power. The concentration of active substance in homeopathic resonation is higher or lower. which is non-toxic. The concentration of the resonator is adjusted at high polarity. The process is an electrolytic process. The active substance and/or the broad band resonator and/or the polar carrier substance are separated from one another by diluents and subjected to a homeopathic power procedure and the process is carried out by contacting together, preferably by the homeopathic procedure (spilling process). The active substance and/or the broad band resonator and/or the polar carrier substance are separated from one another by diluents in different mass and magnification; where the diluent degree is an algorithm of each other, such that each diluent and/or exponentiation step is relative to the stronger diluent of the broad band resonator. The broadband resonator and the polar carrier substance are separated from one another in different steps where the concentration differs by increasing the diluent, preferably decreases in non-linear form.

ORGANIC CHEMISTRY - Preferred Components: The polar carrier substance contains monopolar, preferably acidic or basic carrier substance and at least a natural/synthetic active substance (preferably mineral, vegetable or animal active substance). The polar carrier substance is an acidic, basic or alcoholic solution, where dilution of the solution from one or more polar solvents, preferably on water basis and/or alcoholic basis. The diluent is particularly so intense, that the acidic, basic or alcoholic component is no longer provable. The polar carrier substance comprises at least a physiological component in the body, in acidic form such as salt acid, sulfuric acid, phosphoric acid, ascorbic acid, citric acid or orotic acid; or in basic, preferably sodium carbonate or potassium carbonate. The minus polar component comprises a cation element such as potassium, calcium, sodium, magnesium, preferably carbonate, hydrogen carbonate, hydroxide, hydroxide carbonate or chloride. The concentration of the broadband resonator is 0-10 vol.%, preferably 0-1 vol.%; or less than of 10 wt.%, preferably 0.1 wt.%. The polar carrier substance and/or the output substance in diluted preparations exhibits pH of 5.5, preferably 12-13.5 and alcoholic component concentration of 5-70 vol.%. The active substance is vegetable/animal origin or produce synthetically. The one or more organic/inorganic gelling agents are methylcellulose, alginate, agar-agar, xanthane gum, carob seed grain flour, guar flour or silicic acid-gel. The basic- or minus components comprises iron, copper, chrome or manganese on the basis metals or its compound, which is renounced. The active substance and/or care substance comprises at least one substance such as allantoin, ascorbic acid, vitamin A, sun guard filter, zinc, aloe vera, vitamin E, pantothenic acid, vegetable oils, jojoba oil, olive oil or essential fatty acids. The active substance comprises at least a vegetable active agent and/or vegetable tincture. The secondary plant material contains vitamins and/or enzymes. The basic pH is neutralized by addition of acid.

PHARMACEUTICALS - Preferred Components: (I) exhibits an isotonic solution, preferably for injection. (II) exhibits positive-preparation with acidic carrier substance and negative-preparation with basic carrier substance. The negative-preparation and positive-preparation contains liquid and/or semi liquid preparation, preferably formulated as a cream, lotion or ointment. (I) exhibits a solution of (homeopathic tincture) of broadband resonator and polar carrier substance with the same-/different-polarity and different pH, where the characteristic is different. The pigmentation factor iron and copper exhibits a concentration of 1 wt.%, preferably

1-0.01 wt.%, where (I) is formulated as emulsion, ointment, cream, lotion, preferably in acidic and contains natural salts and/or acidic fraction. The amount of mineral is up to 60 wt.%, preferably 0.5-20 wt.%, where the electrolytic yield of the mineral salt solution as broadband resonator and/or quartz salt is on the basic fraction of natural and/or synthetic. The active substance comprising mineral and plant active substance is formulation as ointment, preferably in 2-3 to 2-7 times. Preferred Composition: (I) further comprises: at least one or more ferromagnetic components and/or compounds (preferably iron, cobalt or nickel); one or more ethereal oil, preferably perfume oil and/or preservative; and iron, zinc and copper as a broad band resonator at a concentration not more than 3 wt.%, preferably 1-0.01 wt.%, where (I) is particularly carried out as hydrophilic oil, oil-alcohol solution, emulsion, salt, cream or lotion; at least an organ preparation and/or organ extraction of animal organ comprises preferably pituitary, cerebrum, thyroid, thymus gland, adrenal glands, gonad, lung, liver, kidneys, small intestine, large intestine, heart, or skin; at least a hormone and/or hormonal tissue and/or neurotransmitter, preferably **thyroxin**, tri iodothyronine, gluco- and mineral corticoid, serotonine, dopamine, heparin or histamine, and masculine and/or feminine sexual hormones as anticonceptive.
INORGANIC CHEMISTRY - Preferred Components: The broadband resonator comprises one or more components such as minerals, trace elements, emulsifying agents, gelling agent, essential/non-essential metals/metal salts and/or nonmetals (preferably quartz sand), stone flour, mineral flour, natural salts (preferably sea salt), rock salt or himalaja salt, shell limestone, healing earth, silicon compound, methyl cellulose, alginate, agar-agar, carob seed grain flour, guar flour, silicic acid, iron, zinc, copper, manganese, chrome, molybdenum, vanadium, nickel, tin, silver, gold, iodine, arsenic, silicon, calcium, magnesium, potassium, sodium or germanium, preferably iron and/or iron compound. (I) comprises minimum 5, preferably 15 different components (preferably of mineral components, heavy metal and/or its compounds). (I) comprises at least an schuessler salt and/or at least fluorescence stream.
INSTRUMENTATION AND TESTING - Preferred Components: The broadband resonator comprises plus- and minus-resonator. The concentration of the broadband resonator in a dilution of homeopathic potency is D3-D23, preferably D12-D23. The concentration of the carrier substance or the broadband resonator is adjusted to a ratio of high polarity. The concentration ratio of active substance or active substance of the broadband resonator is greater than 5:1, preferably 1000000:1. The pH of (I) is 8-12.5, preferably 9-10.5; or 5.5, preferably 2-3.5. Preferred Process: (I) is carried out by homeopathic process after administering dimethyl amino azo benzene (DAB), preferably exponential process, particularly in low, middle or higher decimal power or centesimal power, preferably homeopathic chemical dispensary process. (I) is produced by information, energitizing, oscillation, bioresonance, radionic and/or magnetizing method. The broad band resonator used for organ preparation is a multiresonator or an organic resonator. The broadband resonator and/or the active substance are brought into contact to avoid interaction with liposome. The first step exhibits a low concentration or the resonator and/or a high polarity/resonator concentration ratio and further exhibits high concentration or resonator and/or lower polarity/resonator concentrations ratios and/or low polarities. The interaction between specific active substance and/or the resonator and/or the energetic ratio forms the tissues and structures. The resonator concentration conforms the active agent concentration, preferably in over decimal powers or under the active substance power. The concentration of active substance in homeopathic resonation is higher or lower. which is non-toxic. The concentration of the resonator is adjusted at high polarity. The process is an electrolytic process. The active substance and/or the broad band

resonator and/or the polar carrier substance are separated from one another by diluents and subjected to a homeopathic power procedure and the process is carried out by contacting together, preferably by the homeopathic procedure (spilling process). The active substance and/or the broad band resonator and/or the polar carrier substance are separated from one another by diluents in different mass and magnification; where the diluent degree is an algorithm of each other, such that each diluent and/or exponentiation step is relative to the stronger diluent of the broad band resonator. The broadband resonator and the polar carrier substance are separated from one another in different steps where the concentration differs by increasing the diluent, preferably decreases in non-linear form.

ORGANIC CHEMISTRY - Preferred Components: The polar carrier substance contains monopolar, preferably acidic or basic carrier substance and at least a natural/synthetic active substance (preferably mineral, vegetable or animal active substance). The polar carrier substance is an acidic, basic or alcoholic solution, where dilution of the solution from one or more polar solvents, preferably on water basis and/or alcoholic basis. The diluent is particularly so intense, that the acidic, basic or alcoholic component is no longer provable. The polar carrier substance comprises at least a physiological component in the body, in acidic form such as salt acid, sulfuric acid, phosphoric acid, ascorbic acid, citric acid or orotic acid; or in basic, preferably sodium carbonate or potassium carbonate. The minus polar component comprises a cation element such as potassium, calcium, sodium, magnesium, preferably carbonate, hydrogen carbonate, hydroxide, hydroxide carbonate or chloride. The concentration of the broadband resonator is 0-10 vol.%, preferably 0-1 vol.%; or less than of 10 wt.%, preferably 0.1 wt.%. The polar carrier substance and/or the output substance in diluted preparations exhibits pH of 5.5, preferably 12-13.5 and alcoholic component concentration of 5-70 vol.%. The active substance is vegetable/animal origin or produce synthetically. The one or more organic/inorganic gelling agents are methylcellulose, alginate, agar-agar, xanthane gum, carob seed grain flour, guar flour or silicic acid-gel. The basic- or minus components comprises iron, copper, chrome or manganese on the basis metals or its compound, which is renounced. The active substance and/or care substance comprises at least one substance such as allantoin, ascorbic acid, vitamin A, sun guard filter, zinc, aloe vera, vitamin E, pantothenic acid, vegetable oils, jojoba oil, olive oil or essential fatty acids. The active substance comprises at least a vegetable active agent and/or vegetable tincture. The secondary plant material contains vitamins and/or enzymes. The basic pH is neutralized by addition of acid.

PHARMACEUTICALS - Preferred Components: (I) exhibits an isotonic solution, preferably for injection. (II) exhibits positive-preparation with acidic carrier substance and negative-preparation with basic carrier substance. The negative-preparation and positive-preparation contains liquid and/or semi liquid preparation, preferably formulated as a cream, lotion or ointment. (I) exhibits a solution of (homeopathic tincture) of broadband resonator and polar carrier substance with the same-/different-polarity and different pH, where the characteristic is different. The pigmentation factor iron and copper exhibits a concentration of 1 wt.%, preferably 1-0.01 wt.%, where (I) is formulated as emulsion, ointment, cream, lotion, preferably in acidic and contains natural salts and/or acidic fraction. The amount of mineral is up to 60 wt.%, preferably 0.5-20 wt.%, where the electrolytic yield of the mineral salt solution as broadband resonator and/or quartz salt is on the basic fraction of natural and/or synthetic. The active substance comprising mineral and plant active substance is formulation as ointment, preferably in 2-3 to 2-7 times. Preferred Composition: (I) further comprises: at least one or more ferromagnetic components and/or compounds (preferably iron, cobalt or nickel); one or

more ethereal oil, preferably perfume oil and/or preservative; and iron, zinc and copper as a broad band resonator at a concentration not more than 3 wt.%, preferably 1-0.01 wt.%, where (I) is particularly carried out as hydrophilic oil, oil-alcohol solution, emulsion, salt, cream or lotion; at least an organ preparation and/or organ extraction of animal organ comprises preferably pituitary, cerebrum, thyroid, thymus gland, adrenal glands, gonad, lung, liver, kidneys, small intestine, large intestine, heart, or skin; at least a hormone and/or hormonal tissue and/or neurotransmitter, preferably **thyroxin**, tri iodothyronine, gluco- and mineral corticoid, serotonine, dopamine, heparin or histamine, and masculine and/or feminine sexual hormones as anticonceptive.

ABEX ADMINISTRATION - (I) is in form of liquid or semi-liquid preparation, such as solution, injection, suspension, gel, emulsion, gel emulsion, cream, ointment, liniment, hydrophilic oil, suppositories, powder, soft or hard **gelatin** capsule, tablets, dragees, globule or in capsule are formulated; or in liposome form. (I) is administered in the form of ointment for 2-3 to 2-7 times (all claimed).

L86 ANSWER 15 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2006-038440 [04] WPIX
CROSS REFERENCE: 2005-736465
DOC. NO. CPI: C2006-013778 [04]
TITLE: New polymeric cascade prodrug (comprising an amine containing biologically active moiety and a masking group having at least one nucleophile and being distinct from the carrier) useful as a therapeutic agent
DERWENT CLASS: A96; B05
INVENTOR: HERSEL U; RAU H; SCHNEPF R; VETTER D; WEGGE T; HERSEL U C B G; RAU H C B G; SCHNEPF R C B G; VETTER D C B G; WEGGE T C B G
PATENT ASSIGNEE: (COMP-N) COMPLEX BIOSYSTEMS GMBH
COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2005099768	A2	20051027	(200604)*	EN	117	[11]
EP 1625855	A1	20060215	(200613)	EN		
EP 1732607	A2	20061220	(200702)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005099768	A2	WO 2005-EP3061	20050322
EP 1625855	A1	EP 2004-19293	20040813
EP 1732607	A2	EP 2005-716306	20050322
EP 1732607	A2	WO 2005-EP3061	20050322

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
EP 1732607	A2	Based on	WO 2005099768	A

PRIORITY APPLN. INFO: EP 2004-19293 20040813
EP 2004-75892 20040323
GB 2004-15043 20040705
INT. PATENT CLASSIF.:

IPC ORIGINAL: A61K0047-48 [I,A]; A61K0047-48 [I,C]
IPC RECLASSIF.: A61K0047-48 [I,A]; A61K0047-48 [I,C]
BASIC ABSTRACT:

WO 2005099768 A2 UPAB: 20060116

NOVELTY - Polymeric cascade prodrug (I) (comprising an amine containing biologically active moiety (1) and a masking group having at least one nucleophile (2) and being distinct from the carrier) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) the preparation of (I); (2) a method for hydrolyzing (I) comprising a step of placing (I) in solution with a pH of approximately 7.4; (3) a method of administering an amine-containing moiety to a living organism comprising providing (I); administering (II) to the living organism; and cleaving the amine-containing moiety from the polymeric cascade prodrug by means of a substantially non-enzymatic reaction; and

(4) a method of providing a therapeutically useful concentration of a biologically active molecule by in vivo cleavage of the biologically active molecule from (I).

USE - (I) is useful as a therapeutic agent.

ADVANTAGE - The large amount of (I) is administered in a single dose without concomitant side effects and over dosing. (I) reduces the necessity of repeated and frequent administration of (I). MANUAL CODE: CPI: A10-E01; A12-V01; B02-D; B02-K; B02-N; B02-S;

B04-B03C; B04-C01; B04-C02; B04-C03; B04-H02; B04-H05; B04-H15; B04-J03; B04-J04; B04-J05; B04-J10; B04-J12; B04-L01; B04-N02; B06-H; B07-H; B08-D02; B09-D01; B10-A04; B10-A08; B10-A10; B10-A11B; B10-A13D; B10-B01B; B10-B02E; B10-B03B

TECH

ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises synthesizing at least one intermediate compound (3) from the aryl compounds of formula (II); and attaching an amine-containing biologically active moiety D to (3) to form the polymeric prodrug. Preferred Components: The first intermediate is aryl compounds of formula (III) (which is synthesized by acylating Y2 with nucleophile compound of formula Nu-W1-Y4-C=Y1, and optionally attaching a first protecting group PG1); the second intermediate is aryl compounds of formula (IV), which is formed by activating (III) with an activating agent (where the amine-containing biologically active moiety D is attached to IV by displacement of the leaving group A, and the method comprises a step of removal of the reversible first protecting group PG1 from (IV) in the presence of a reagent (trifluoroacetic acid or DTT) and the removal step further comprises a step of attaching a polymer R1 to X)). The polymeric cascade prodrug linker reagent is aryl compounds of formula (A). The solution is an extra-cellular fluid. Preferred Process: The preparation of (III) further comprises a step of removing the first polymer protection group PG1 and attaching polymer R1 to X to form a third aryl intermediate compounds of formula (VI); and activating the (VI) by using activating agent to form a fourth aryl intermediate compounds of formula (VII) (where the amine-containing biologically active moiety D is attached to VII by displacement of the leaving group A; and the method comprises a step of reacting (II) with a first polymer R1 to attach the first polymer R1 to X; a step of protecting Y2 with a second protective group PG2; activating the prodrug with an activating agent and reacting with an amine-containing biologically active moiety D to form a fifth aryl intermediate compounds of formula (X)). Preparation of (I) comprises a step of attaching a removable first protecting group PG1 to X and a removable second protecting group PG2 to (II) followed by activation using an activating agent to form sixth aryl intermediate compounds of formula (VIII) (where the amine-containing biologically active moiety D is attached to VIII by displacement of the leaving group A; and the method comprises a step of

removing the first protecting group PG1 from X and attaching a polymer R1, and the second protecting group PG2 is removed by Y2, which is acylated with formula Nu-W1-Y4-C=Y1). The preparation of (I) further comprises a step of activating (III) by using an activating agent to form (VII) (where the amine-containing biologically active moiety D is attached to VII by displacement of the leaving group A). The activating agent is 4-nitrophenyl chloroformate or disuccinyl carbonate. The second protecting group PG2 is removed from Y2, which is acylated with formula Nu-W1-Y4-C=Y1. (II) is replaced by ring compounds of formula (IIb) (where R2 is cyclical alkyls or heteroalkyl heteroaryl (all optionally substituted), H, aryls, CN, NO2, halo, carboxy, carboxyalkyl, alkylcarbonyl or carboxamidoalkyl). In the method of administering (I), the cleavage step is carried out in an extra-cellular fluid. The non-enzymatic reaction comprises a step of hydrolysis, a step intramolecular cyclization or intramolecular catalysis. The method of administering (I) further comprises a step of sterically protecting at least part of the linker by a sterically demanding carrier. The method of cleaving the amine-containing moiety from the carrier by a substantially non-enzymatic reaction of the nucleophile-containing linker. The non-enzymatic reaction is carried out at a pH of 7.4. The amine-containing moiety attached to the carrier is cleaved in an extra-cellular fluid. The method of cleaving the amine-containing moiety from the carrier, further comprises a step of sterically protecting at least part of the nucleophile-containing linker by a sterically demanding carrier. The amine containing moiety is a biologically active moiety.

T = D or A;

D = a residue of an amine containing biologically active moiety;

A = a leaving group (preferably chloride, bromide, fluoride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy or N-hyroxysulfosuccinimidyl);

X = a spacer moiety such as R5-Y6;

Y1, Y2 = O, S or NR6;

Y3, Y5 = O or S;

Y4 = O, NR6, or -C(R7)(R8)-;

Y6 = O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or any heteroatom containing a free electron pair or is absent;

R3 = H, optionally substituted alkyl, cycloalkyl or heteroalkyl, aryls (substituted), heteroaryl(substituted), CN, NO2, halo, carboxy, carboxyalkyl, alkylcarbonyl or carboxamidoalkyl;

R4 = heteroaryl, alkyl, cycloalkyl, alkoxy, cycloalkoxy, cycloheteroalkyloxy (all optionally substituted), H, heteroalkyl, aryl (substituted), aryloxy, heteroaryloxy, CN or halo (preferably H, CH3, ethyl, ethoxy, methoxy, and other linear alkyls, cyclo alkyls or branched alkyls and heteroalkyl comprising one to six carbon atoms);

R5 = alkyl, cycloalkyl or heteroalkyl, heteroaryl (all optionally substituted) or aryl(substituted);

R7, R8 = alkyl, cycloalkyl or heteroalkyl, heteroaryl (all optionally substituted), H, aryl(substituted), carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, CN or halo;

R6 = alkyl, cycloalkyl, heteroaryls or heteroalkyl (all optionally substituted), H, aryl(substituted);

R1 = a polymer (preferably polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid or its derivatives, alginate, xylan, mannan, carrageenan, agarose, cellulose, starch, hydroxyethyl starch (HES) and other carbohydrate-based polymers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamides) such as poly(hydroxypropylmethacrylamide) (HMPA), poly(acrylates), poly(methacrylates) like poly(hydroxyethylmethacrylate),

poly(organophosphazenes), poly(siloxanes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid), collagen, **gelatin**, copolymers, grafted copolymers, cross-linked polymers, or their block copolymers (preferably hydrogel, branched or hyper branched polymer, dendrimer or dense star polymer, a protein or a biopolymer)) (where R1 further includes biologically active substances, the polymer of R1 has at least one functional group (carboxylic acid and activated derivatives, amino, maleimide, thiol, sulfonic acid and derivatives, carbonate and derivatives, carbamate and derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane, or aziridine) for linkage to X);
W1 = alkyl, cycloalkyl, cycloheteroalkyl, heteroaryls (all optionally substituted) or aryl(substituted);
Nu = a nucleophile (preferably nucleophiles consisting of primary, secondary and tertiary amino groups, thiol, carboxylic acid, hydroxylamine, hydrazine or nitrogen containing heteroaryl);
n = 0 or a positive integer; and
Ar = a multi-substituted aromatic hydrocarbon or aromatic heterocycle (preferably 18 heteroaryl compounds e.g. disubstituted phenyl, disubstituted naphthalenyl, disubstituted pyrimidine or disubstituted pyridine, where W is O, S or N).
The bond or group formed between X and R1 is bonds or groups consisting of carbamate, S-succinimido, urea, amide (all preferred), amino, carboxylic ester, sulfonamide, disulfide, carbonate, there, oxime, hydrazone, thiourea, phosphate or phosphonate; In (A), T is a leaving group A for covalent conjugation with a biologically active moiety (preferably peptide, polypeptide or protein).
POLYMERS - (1) is biologically moieties consisting of small molecule biologically active agents or biopolymers (biopolymers consisting of proteins, polypeptides, oligonucleotides or peptide nucleic acids). The polypeptides are polypeptides consisting of ACTH, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides like GLP-1, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2, 3, 4, 6, 10, 11, 12), interleukin (IL)-1 receptor antagonist (rti1L-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-A.H), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator

(tPA), TSH, urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is (a protein prepared by recombinant DNA technology) antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins (preferably antibodies, calcitonin, G-CSF, GM-CSF, erythropoietins, hemoglobins, interleukins, insulins, interferons, SOD, somatropin, tumor necrosis factor (TNF), TNF-receptor-immunogluobulin C Fc, glucagon-like peptides HkeGLP-1). The small molecule biologically active agents are central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, or cardiovascular agents with at least one primary or secondary amino group (preferably daunorubicin, doxorubicin, idarubicin, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxacin, noxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamine, dobutamin, lisinopril, serotonin, acivicin or carbutamid).

ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises synthesizing at least one intermediate compound (3) from the aryl compounds of formula (II); and attaching an amine-containing biologically active moiety D to (3) to form the polymeric prodrug. Preferred Components: The first intermediate is aryl compounds of formula (III) (which is synthesized by acylating Y2 with nucleophile compound of formula Nu-W1-Y4-C=Y1, and optionally attaching a first protecting group PG1); the second intermediate is aryl compounds of formula (IV), which is formed by activating (III) with an activating agent (where the amine-containing biologically active moiety D is attached to IV by displacement of the leaving group A, and the method comprises a step of removal of the reversible first protecting group PG1 from (IV) in the presence of a reagent (trifluoroacetic acid or DTT) and the removal step further comprises a step of attaching a polymer R1 to X)). The polymeric cascade prodrug linker reagent is aryl compounds of formula (A). The solution is an extra-cellular fluid. Preferred Process: The preparation of (III) further comprises a step of removing the first polymer protection group PG1 and attaching polymer R1 to X to form a third aryl intermediate compounds of formula (VI); and activating the (VI) by using activating agent to form a fourth aryl intermediate compounds of formula (VII) (where the amine-containing biologically active moiety D is attached to VII by displacement of the leaving group A; and the method comprises a step of reacting (II) with a first polymer R1 to attach the first polymer R1 to X; a step of protecting Y2 with a second protective group PG2; activating the prodrug with an activating agent and reacting with an amine-containing biologically active moiety D to form a fifth aryl intermediate compounds of formula (X)). Preparation of (I) comprises a step of attaching a removable first protecting group PG1 to X and a removable second protecting group PG2 to (II) followed by activation using an activating agent to form sixth aryl intermediate compounds of formula (VIII) (where the amine-containing biologically active moiety D is attached to VIII by displacement of the leaving group A; and the method comprises a step of removing the first protecting group PG1 from X and attaching a polymer R1, and the second protecting group PG2 is removed by Y2, which is acylated with formula Nu-W1-Y4-C=Y1). The preparation of (I) further comprises a step of activating (III) by using an activating agent to form (VII) (where the amine-containing biologically active moiety D is attached to VII by displacement of the leaving group A). The activating agent is 4-nitrophenyl chloroformate or disuccinyl carbonate. The second protecting group PG2 is removed from Y2, which is acylated with formula Nu-W1-Y4-C=Y1. (II) is replaced by ring compounds of formula (IIb) (where R2 is cyclical alkyls or heteroalkyl heteroaryl (all optionally substituted), H, aryls, CN, NO2, halo, carboxy, carboxyalkyl,

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Y1, Y2 = O, S or NR6;
Y3, Y5 = O or S;
Y4 = O, NR6, or -C(R7)(R8)-;
Y6 = O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or any heteroatom containing a free electron pair or is absent;
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hydrazine, isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane, or aziridine) for linkage to X);
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The bond or group formed between X and R1 is bonds or groups consisting of carbamate, S-succinimido, urea, amide (all preferred), amino, carboxylic ester, sulfonamide, disulfide, carbonate, there, oxime, hydrazone, thiourea, phosphate or phosphonate; In (A), T is a leaving group A for covalent conjugation with a biologically active moiety (preferably peptide, polypeptide or protein).
POLYMERS - (1) is biologically moieties consisting of small molecule biologically active agents or biopolymers (biopolymers consisting of proteins, polypeptides, oligonucleotides or peptide nucleic acids). The polypeptides are polypeptides consisting of ACTH, adenosine deaminase, agalsidase, albumin, alfa-1 antitrypsin (AAT), alfa-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor VIII, factor VIIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucagon-like peptides like GLP-1, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1 alfa, 1 beta, 2, 3, 4, 6, 10, 11, 12), interleukin (IL)-1 receptor antagonist (rti1L-1ra), insulins, interferons (alfa 2a, alfa 2b, alfa 2c, beta 1a, beta 1b, gamma 1a, gamma 1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-A.H), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), TSH, urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is (a protein prepared by recombinant DNA technology) antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins (preferably antibodies, calcitonin, G-CSF, GM-CSF, erythropoietins, hemoglobins, interleukins, insulins, interferons, SOD, somatropin, tumor necrosis factor (TNF), TNF-receptor-immunogluobulin C Fc, glucagon-like peptides HkeGLP-1). The small molecule biologically active agents are central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, or cardiovascular agents with at least one primary or secondary amino group

(preferably daunorubicin, doxorubicin, idarubicin, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxacin, noxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamine, dobutamin, lisinopril, serotonin, acivicin or carbutamid).

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DCR: 104211-K 104211-M 104211-P 104211-Q 203311-K 203311-M
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DCN: R01879-K R01879-M R01879-P R01879-Q
DCR: 109946-K 109946-M 109946-P 109946-Q 109946-S 109946-U
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DCR: 107856-K 107856-M 107856-P 107856-Q
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DCR: 107436-K 107436-M 107436-P 107436-Q
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DCN: RA02HP-K RA02HP-M RA02HP-P RA02HP-Q
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DCR: 104749-K 104749-M 104749-P 104749-Q
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DCR: 103599-K 103599-M 103599-P 103599-Q
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DCN: RA063L-K RA063L-M RA063L-P RA063L-Q
DCR: 104225-K 104225-M 104225-P 104225-Q
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DCN: RA078P-K RA078P-M RA078P-P RA078P-Q
DCR: 103220-K 103220-M 103220-P 103220-Q
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DCR: 132752-K 132752-M 132752-P 132752-Q
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DCN: RA022K-K RA022K-M RA022K-P RA022K-Q
DCR: 97854-K 97854-M 97854-P 97854-Q
M1 *19* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: R01851-K R01851-M R01851-P R01851-Q R06675-K R06675-M R06675-P R06675-Q
DCR: 97834-K 97834-M 97834-P 97834-Q
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DCR: 96948-K 96948-M 96948-P 96948-Q
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M1 *36* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R24039-K R24039-M R24039-P R24039-Q
DCR: 86886-K 86886-M 86886-P 86886-Q

M1 *37* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA013I-K RA013I-M RA013I-P RA013I-Q
DCR: 184610-K 184610-M 184610-P 184610-Q

M1 *38* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA00H1-K RA00H1-M RA00H1-P RA00H1-Q
DCR: 1012046-K 1012046-M 1012046-P 1012046-Q 184611-K 184611-M 184611-P 184611-Q

M1 *39* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA00H3-K RA00H3-M RA00H3-P RA00H3-Q
DCR: 184616-K 184616-M 184616-P 184616-Q

M1 *40* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R01857-K R01857-M R01857-P R01857-Q R16573-K R16573-M R16573-P R16573-Q
DCR: 92818-K 92818-M 92818-P 92818-Q 92818-S 92818-U

M1 *41* H4 H402 H482 H5 H589 H8 M280 M313 M323 M332 M342 M383 M393 M423 M431 M510 M520 M530 M540 M620 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R23531-K R23531-M R23531-P R23531-Q
DCR: 104472-K 104472-M 104472-P 104472-Q

M1 *42* H4 H402 H482 H5 H589 H8 M280 M312 M323 M332 M342 M383 M393 M416 M423 M431 M510 M520 M530 M540 M620 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R02044-K R02044-M R02044-P R02044-Q RA0GM6-K RA0GM6-M RA0GM6-P RA0GM6-Q
DCR: 900-K 900-M 900-P 900-Q 900-S 900-U 99962-K 99962-M 99962-P 99962-Q

M1 *43* F012 F013 F014 F016 F019 F123 F199 H1 H100 H121 H4 H404 H405 H421 H422 H423 H424 H482 H483 H484 H581 H582 H583 H584 H589 H8 K0 L8 L814 L821 L822 L823 L824 L834 M280 M311 M323 M342 M373 M393 M413 M423 M431 M510 M521 M522 M523 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R03882-K R03882-M R03882-P R03882-Q R07813-K R07813-M R07813-P R07813-Q
DCR: 104328-K 104328-M 104328-P 104328-Q

M1 *44* J0 J011 J1 J111 J3 J321 K0 L8 L814 L824 L832 L834 M210 M211 M262 M280 M281 M320 M423 M431 M720 M782 M800 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R03231-K R03231-M R03231-P R03231-Q R06437-K R06437-M R06437-P R06437-Q
DCR: 97115-K 97115-M 97115-P 97115-Q

M1 *45* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA04J1-K RA04J1-M RA04J1-P RA04J1-Q

DCR: 86923-K 86923-M 86923-P 86923-Q

M1 *46* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA0RON-K RA0RON-M RA0RON-P RA0RON-Q
DCR: 110651-K 110651-M 110651-P 110651-Q

M1 *47* F012 F013 F014 F015 F016 F019 F123 F199 H4 H405 H424 H481 H5 H521 H8 M280 M311 M322 M342 M373 M392 M413 M423 M431 M510 M522 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA0XRQ-K RA0XRQ-M RA0XRQ-P RA0XRQ-Q
DCR: 100074-K 100074-M 100074-P 100074-Q

M1 *48* A220 A960 C710 K0 K4 K421 L8 L815 L831 M423 M431 M630 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R24036-K R24036-M R24036-P R24036-Q
DCR: 90114-K 90114-M 90114-P 90114-Q

M1 *49* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA05MC-K RA05MC-M RA05MC-P RA05MC-Q
DCR: 86730-K 86730-M 86730-P 86730-Q

M1 *50* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R01852-K R01852-M R01852-P R01852-Q
DCR: 135415-P 135415-S 135415-U 90356-K 90356-M 90356-P 90356-Q 90356-S 90356-U

M1 *51* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R01863-K R01863-M R01863-P R01863-Q
DCR: 107779-K 107779-M 107779-P 107779-Q 107779-S 107779-U

M1 *52* H4 H401 H481 H7 H713 H721 H8 M210 M212 M272 M281 M320 M423 M431 M510 M520 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA01EA-K RA01EA-M RA01EA-P RA01EA-Q
DCR: 104492-K 104492-M 104492-P 104492-Q

M1 *53* K0 L4 L463 L499 M280 M312 M313 M314 M315 M323 M332 M342 M383 M393 M423 M431 M510 M520 M530 M540 M620 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R16492-K R16492-M R16492-P R16492-Q
DCR: 104486-K 104486-M 104486-P 104486-Q

M1 *54* H7 H714 H721 J0 J011 J1 J171 M210 M212 M262 M281 M320 M423 M431 M510 M520 M530 M540 M630 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA02L0-K RA02L0-M RA02L0-P RA02L0-Q RA037T-K RA037T-M RA037T-P RA037T-Q
DCR: 104380-K 104380-M 104380-P 104380-Q 199392-K 199392-M 199392-P 199392-Q

M1 *55* H7 H714 H721 J0 J011 J3 J371 M210 M212 M262 M281 M320 M423 M431 M510 M520 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA035M-K RA035M-M RA035M-P RA035M-Q
DCR: 104379-K 104379-M 104379-P 104379-Q

M1 *56* H7 H714 H721 J0 J011 J1 J171 M210 M213 M262 M281 M320 M423 M431 M510 M520 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA07AE-K RA07AE-M RA07AE-P RA07AE-Q
DCR: 104431-K 104431-M 104431-P 104431-Q

M1 *57* H4 H401 H481 H7 H721 H8 J0 J011 J2 J271 M210 M212 M262 M281 M312 M321 M332 M342 M383 M391 M423 M431 M510 M520 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA01SA-K RA01SA-M RA01SA-P RA01SA-Q
DCR: 104421-K 104421-M 104421-P 104421-Q

M1 *58* B414 B702 B712 B720 B744 B798 B833 C108 C800 C802 C803 C804 C805 C807 M210 M211 M250 M283 M320 M411 M423 M431 M510 M520 M530 M540 M620 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904

DCN: RA012F-K RA012F-M RA012F-P RA012F-Q
DCR: 107032-K 107032-M 107032-P 107032-Q
M1 *59* F012 F013 F423 H7 H715 H721 J5 J521 L9 L941 M210 M212 M240 M281 M320 M423 M431 M510 M521 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA00D5-K RA00D5-M RA00D5-P RA00D5-Q
DCR: 1062-K 1062-M 1062-P 1062-Q
M1 *60* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R24034-K R24034-M R24034-P R24034-Q
DCR: 91481-K 91481-M 91481-P 91481-Q
M1 *61* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R24033-K R24033-M R24033-P R24033-Q
DCR: 95972-K 95972-M 95972-P 95972-Q
M1 *62* M423 M431 M720 M782 N222 N252 N263 N352 N383 N512 M905
DCN: RA00I9-K RA00I9-M RA00I9-P RA00I9-Q
DCR: 184613-K 184613-M 184613-P 184613-Q
M1 *90* C009 C017 C035 C316 D011 D021 D810 F010 F011 F012 F013 F014 F015 F019 F020 F021 F029 F422 F423 F499 F521 G001 G002 G003 G010 G011 G012 G013 G014 G015 G016 G018 G019 G020 G021 G022 G029 G030 G031 G032 G039 G040 G050 G051 G100 G111 G112 G113 G221 G299 G553 G563 H100 H102 H103 H121 H141 H161 H181 H211 H212 H341 H381 H401 H402 H403 H404 H405 H461 H462 H463 H464 H521 H522 H523 H541 H542 H543 H561 H581 H592 H594 H600 H601 H608 H609 H621 H622 H623 H641 H642 H643 H682 H683 H684 H689 H713 H715 H716 H721 H722 H723 H731 H732 J011 J012 J013 J014 J171 J172 J173 J211 J221 J231 J241 J271 J290 J321 J341 J371 J372 J373 J390 J522 J523 J581 J582 J583 K442 K620 K640 K820 K850 K899 L142 L143 L145 L199 L250 L260 L270 L280 L290 L310 L320 L340 L352 L410 L420 L431 L432 L440 L450 L461 L462 L463 L471 L472 L499 L511 L531 L541 L599 L640 L650 L660 L930 L999 M111 M112 M113 M114 M115 M116 M119 M121 M122 M123 M124 M125 M126 M129 M132 M135 M137 M139 M141 M143 M149 M150 M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225 M226 M231 M232 M233 M240 M261 M262 M263 M272 M280 M281 M282 M283 M311 M312 M313 M314 M315 M316 M320 M321 M322 M323 M331 M332 M333 M334 M340 M342 M343 M344 M349 M351 M352 M371 M372 M373 M381 M391 M412 M413 M414 M423 M431 M510 M511 M520 M521 M522 M523 M530 M531 M532 M533 M540 M541 M542 M543 M710 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
MCN: 0208-85401-M 0208-85401-N 0208-85401-P 0208-85401-Q
M2 *63* F012 F014 F015 F016 F123 G020 G022 G029 G034 G038 G420 H1 H100 H121 H4 H404 H421 H442 H461 H5 H521 H541 H8 J5 J581 K0 L8 L817 L821 L834 L9 L951 M1 M126 M141 M210 M211 M240 M262 M272 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R06570-K R06570-M R06570-P R06570-Q R08031-K R08031-M R08031-P R08031-Q
DCR: 92292-K 92292-M 92292-P 92292-Q
M2 *64* F012 F013 F014 F016 F123 G020 G022 G029 G034 G038 G420 H1 H100 H121 H4 H405 H421 H442 H461 H481 H5 H521 H541 H8 J5 J581 K0 L8 L817 L821 L834 L9 L951 M1 M126 M141 M210 M211 M240 M272 M281 M311 M321 M342 M349 M381 M391 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R02028-K R02028-M R02028-P R02028-Q R08024-K R08024-M R08024-P R08024-Q
DCR: 142654-P 142654-S 142654-U 8769-K 8769-M 8769-P 8769-Q 8769-S 8769-U
M2 *65* F012 F013 F014 F016 F123 G022 G029 G034 G038 G420 H1 H100 H121 H4 H404 H421 H442 H461 H5 H521 H8 J5 J581 K0 L8 L814 L821 L834 L9 L951 M1 M126 M141 M210 M211 M240 M262 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904

DCN: R08029-K R08029-M R08029-P R08029-Q R08030-K R08030-M R08030-P R08030-Q
DCR: 97647-K 97647-M 97647-P 97647-Q

M2 *66* G022 G029 G331 H1 H102 H142 H182 H4 H404 H442 H482 H8 K0 L9 L951 M280 M312 M323 M332 M342 M383 M393 M414 M431 M510 M520 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R07208-K R07208-M R07208-P R07208-Q
DCR: 101093-K 101093-M 101093-P 101093-Q

M2 *67* F012 F013 F016 F017 F433 G013 G100 H1 H100 H141 J5 J522 L9 L930 M1 M113 M210 M212 M240 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R09886-K R09886-M R09886-P R09886-Q
DCR: 87239-K 87239-M 87239-P 87239-Q

M2 *68* G060 G740 H1 H100 H161 M280 M320 M415 M431 M510 M520 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
RIN: 03624
DCN: R01452-K R01452-M R01452-P R01452-Q R04253-K R04253-M R04253-P R04253-Q
DCR: 87119-K 87119-M 87119-P 87119-Q 87119-S 87119-U

M2 *69* C316 G013 G019 G100 H1 H101 H142 K0 K4 K442 M1 M121 M142 M280 M320 M414 M431 M510 M520 M532 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R00472-K R00472-M R00472-P R00472-Q
DCR: 92280-K 92280-M 92280-P 92280-Q 92280-S 92280-U

M2 *70* H1 H102 H182 H4 H402 H482 H8 M280 M312 M314 M321 M322 M331 M332 M342 M383 M393 M416 M431 M620 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R07733-K R07733-M R07733-P R07733-Q
DCR: 94577-K 94577-M 94577-P 94577-Q

M2 *71* C316 F012 F541 G013 G100 H1 H100 H141 K0 K3 K353 L9 L922 M1 M123 M147 M280 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R00283-K R00283-M R00283-P R00283-Q
DCR: 107025-P 107025-S 107025-U 108000-K 108000-M 108000-P 108000-Q 108000-S 108000-U 130130-P 130130-S 130130-U

M2 *72* C316 F012 F014 F541 G013 G100 H1 H100 H141 K0 K3 K353 L9 L922 M1 M123 M147 M210 M211 M240 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R01088-K R01088-M R01088-P R01088-Q
DCR: 108014-K 108014-M 108014-P 108014-Q 108014-S 108014-U

M2 *73* C316 F013 F015 F620 G013 G100 H1 H100 H141 K0 K3 K353 L9 L943 M1 M123 M147 M210 M211 M240 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R01445-K R01445-M R01445-P R01445-Q R03684-K R03684-M R03684-P R03684-Q
DCR: 108017-K 108017-M 108017-P 108017-Q 108017-S 108017-U

M2 *74* C316 F012 F013 F551 G013 G100 H1 H100 H141 H5 H521 H8 K0 K3 K353 L941 L943 M1 M123 M147 M210 M211 M272 M281 M320 M413 M431 M510 M521 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R19180-K R19180-M R19180-P R19180-Q
DCR: 108011-K 108011-M 108011-P 108011-Q

M2 *75* D014 D024 D622 F011 F013 F423 G030 G530 H1 H100 H121 H141 H161 H2 H202 H6 H601 H602 H642 J0 J011 J1 J111 J5 J521 M280 M320 M412 M431 M511 M521 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RA1YB4-K RA1YB4-M RA1YB4-P RA1YB4-Q
DCR: 91233-K 91233-M 91233-P 91233-Q

M2 *76* D012 D014 D024 D030 D622 D720 G030 G530 H1 H141 H161 H2 H202 H5 H541 H6 H601 H641 H8 J0 J011 J1 J111 J5 J521 M210 M211 M272 M281

M320 M412 M431 M512 M520 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
RIN: 01279
DCN: RA03ZR-K RA03ZR-M RA03ZR-P RA03ZR-Q
DCR: 159480-K 159480-M 159480-P 159480-Q

M2 *77* D014 D023 D622 F011 F553 G030 G530 H1 H141 H161 H2 H202 H6 H601 H641 J0 J011 J1 J111 J5 J521 M280 M320 M412 M431 M511 M521 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R10124-K R10124-M R10124-P R10124-Q
DCR: 91082-K 91082-M 91082-P 91082-Q

M2 *78* D014 D023 D622 F011 F553 H1 H141 H181 H2 H202 H6 H601 H641 J5 J521 M210 M212 M273 M281 M320 M412 M431 M511 M521 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R04550-K R04550-M R04550-P R04550-Q
DCR: 102303-K 102303-M 102303-P 102303-Q

M2 *79* C108 C316 C540 C720 F012 F013 F014 F015 F016 F019 F113 F123 F199 G037 G563 H1 H100 H122 H162 H182 H4 H405 H424 H461 H481 H5 H523 H8 K0 L8 L812 L817 L819 L821 L822 L831 L834 M1 M126 M141 M149 M280 M311 M323 M342 M373 M393 M411 M431 M510 M523 M530 M640 M720 M782 M800 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R06700-K R06700-M R06700-P R06700-Q
DCR: 130511-K 130511-M 130511-P 130511-Q

M2 *80* D013 D025 D030 D240 H1 H102 H162 H4 H403 H421 H462 H8 J5 J521 M210 M211 M240 M273 M281 M282 M320 M412 M431 M511 M520 M530 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
RIN: 12686
DCN: R01571-K R01571-M R01571-P R01571-Q
DCR: 107496-K 107496-M 107496-P 107496-Q 107496-S 107496-U

M2 *81* F012 F013 F014 F015 F016 F019 F123 F199 G037 G563 H1 H100 H101 H121 H162 H181 H4 H405 H424 H461 H481 H5 H522 H8 K0 L8 L814 L823 L833 L834 M1 M126 M129 M141 M149 M280 M311 M322 M342 M373 M392 M413 M431 M510 M522 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R03878-K R03878-M R03878-P R03878-Q
DCR: 98579-K 98579-M 98579-P 98579-Q

M2 *82* D013 D014 D690 F012 F014 F423 H4 H401 H481 H5 H592 H8 H9 J0 J012 J1 J111 J3 J311 J5 J521 L9 L941 M1 M126 M142 M210 M211 M240 M273 M281 M282 M312 M321 M331 M340 M342 M373 M391 M412 M431 M511 M521 M530 M541 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
RIN: 41252
DCN: R23271-K R23271-M R23271-P R23271-Q
DCR: 100514-K 100514-M 100514-P 100514-Q

M2 *83* G015 G100 H1 H100 H181 H4 H402 H442 H8 M280 M312 M321 M332 M342 M373 M391 M414 M431 M510 M520 M531 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: R00053-K R00053-M R00053-P R00053-Q
DCR: 7903-K 7903-M 7903-P 7903-Q 7903-S 7903-U

M2 *84* G013 G015 G100 H1 H102 H181 H4 H403 H443 H8 M280 M312 M314 M321 M331 M332 M342 M373 M392 M414 M431 M510 M520 M532 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R11507-K R11507-M R11507-P R11507-Q R13752-K R13752-M R13752-P R13752-Q
DCR: 93611-K 93611-M 93611-P 93611-Q

M2 *85* F011 F012 F423 G010 G100 H1 H100 H102 H182 H2 H211 J0 J013 J1 J111 J171 J3 J371 M280 M313 M315 M321 M332 M343 M349 M371 M381 M391 M413 M431 M510 M521 M531 M540 M720 M782 M800 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R09697-K R09697-M R09697-P R09697-Q
DCR: 99480-K 99480-M 99480-P 99480-Q

M2 *86* D011 D022 D601 H1 H100 H181 H4 H401 H441 H8 M280 M312 M321 M332

M342 M373 M391 M412 M431 M511 M520 M530 M540 M720 M782 N222 N252
N263 N352 N383 N512 M905 M904 M910
DCN: R00030-K R00030-M R00030-P R00030-Q
DCR: 106919-K 106919-M 106919-P 106919-Q 106919-S 106919-U

M2 *87* F013 F015 F620 H1 H100 H181 H6 H602 H621 J0 J011 J1 J171 M280
M311 M321 M343 M349 M371 M391 M413 M431 M510 M521 M530 M540 M720
M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: R18816-K R18816-M R18816-P R18816-Q
DCR: 86450-K 86450-M 86450-P 86450-Q

M2 *88* C316 G013 G100 H1 H100 H141 K0 K3 K351 L4 L431 M210 M214 M231
M273 M281 M320 M414 M431 M510 M520 M531 M540 M720 M782 N222 N252
N263 N352 N383 N512 M905 M904
DCN: RA1UX3-K RA1UX3-M RA1UX3-P RA1UX3-Q
DCR: 90063-K 90063-M 90063-P 90063-Q

M2 *89* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609
H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343
M349 M371 M391 M414 M431 M510 M520 M532 M540 M720 M782 N222 N252
N263 N352 N383 N512 M905 M904 M910
DCN: **R00050-K R00050-M R00050-P**
R00050-Q R04769-K R04769-M
R04769-P R04769-Q
DCR: **108879-K 108879-M 108879-P**
108879-Q 108879-S 108879-U

M2 *91* G015 G100 H1 H100 H103 H182 H4 H401 H481 H8 J0 J011 J3 J371 K0
L4 L463 M210 M211 M262 M273 M281 M283 M311 M312 M315 M321 M322
M332 M342 M373 M383 M392 M414 M431 M510 M520 M531 M540 M710 M720
M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RAKHUR-M RAKHUR-N RAKHUR-P RAKHUR-Q
DCR: 1202290-M 1202290-N 1202290-P 1202290-Q

M2 *92* F011 F012 F013 F015 F019 F423 F431 G013 G100 H1 H103 H181 H2
H211 H3 H321 J5 J522 K0 K2 K224 K8 K820 L4 L410 L463 L472 L9
L930 M210 M211 M212 M273 M283 M313 M315 M321 M332 M342 M343 M373
M383 M391 M413 M431 M510 M522 M531 M540 M710 M720 M782 N222 N252
N263 N352 N383 N512 M905 M904
DCN: RAKHUS-M RAKHUS-N RAKHUS-P RAKHUS-Q
DCR: 1202291-M 1202291-N 1202291-P 1202291-Q

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M431 M510 M520 M533 M540 M710 M720 M782 N222 N252 N263 N352 N383
N512 M905 M904
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M905 M904
DCN: RAKHUW-M RAKHUW-N RAKHUW-P RAKHUW-Q
DCR: 1202295-M 1202295-N 1202295-P 1202295-Q

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M2 *98* G010 G013 G019 G100 H1 H103 H181 H3 H341 H5 H541 H598 H8 H9 J0 J011 J3 J371 K0 L4 L463 L472 M1 M121 M129 M132 M150 M210 M211 M212 M272 M273 M281 M283 M311 M312 M313 M321 M322 M332 M342 M343 M344 M373 M381 M383 M391 M392 M414 M431 M510 M520 M533 M540 M710 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904
DCN: RAKHUY-M RAKHUY-N RAKHUY-P RAKHUY-Q
DCR: 1202297-M 1202297-N 1202297-P 1202297-Q

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DCN: RAKHUZ-M RAKHUZ-N RAKHUZ-P RAKHUZ-Q
DCR: 1202298-M 1202298-N 1202298-P 1202298-Q

DRN 0030-P 0030-U 0030-S **0050-P 0050-U 0050-S**
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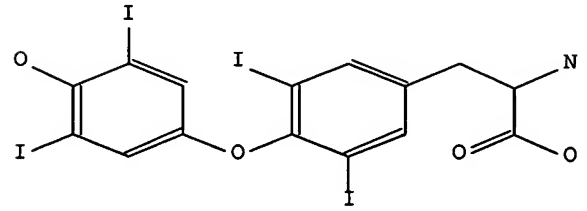
M2 *89* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M720 M782 N222 N252 N263 N352 N383 N512 M905 M904 M910
DCN: **R00050-K R00050-M R00050-P R00050-Q R04769-K R04769-M R04769-P R04769-Q**
DCR: **108879-K 108879-M 108879-P 108879-Q 108879-S 108879-U**

AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 16 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-655654 [67] WPIX
DOC. NO. CPI: C2005-198175 [67]
DOC. NO. NON-CPI: N2005-537041 [67]
TITLE: Medical device, e.g. stent, for drug delivery, comprises biologically active structure having biologically active compounds, attached to stent structure
DERWENT CLASS: A96; B04; B07; D22; P32
INVENTOR: AKHTAR A J; MAHMOOD S A
PATENT ASSIGNEE: (AKHT-I) AKHTAR A J; (MAHM-I) MAHMOOD S A
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20050187607	A1	20050825	(200567)*	EN	22[7]	A61F002-06

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20050187607	A1	US 2004-783727	20040220

PRIORITY APPLN. INFO: US 2004-783727 20040220
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61F0002-06 [I,A]; A61F0002-06 [I,C]
BASIC ABSTRACT:
US 20050187607 A1 UPAB: 20051223
NOVELTY - A medical device comprises a biologically active structure having biologically active compounds, attached to a stent structure.
DETAILED DESCRIPTION - A medical device comprises a stent structure having an outer surface and an inner surface that defines a lumen; and a biologically active structure attached to the stent structure, the biologically active structure having a first layer having a first biologically active compound with a first biological activity, a second layer having a second biologically active compound having a second biological activity, and a third layer located between the first and second layers, where the third layer is impermeable to the first biologically active compound and to the second biologically active compound.
USE - As a medical device, e.g. stent, for drug delivery.
ADVANTAGE - The inventive device is efficient and effective. DESCRIPTION OF DRAWINGS - The figure illustrates a perspective view showing exposed layers of the biologically active structure attached to the outer surface of the stent structure.
MANUAL CODE: CPI: A12-V03B; B01-B02; B01-B03; B01-C05; B02-T; B04-C02; B04-C03; B04-H01; B04-M01; B05-A03B; B05-B01P; B06-A03; B06-D09; B06-D18; B06-E05; B07-D04C; B07-D05; B07-D12; B10-B02A; B10-B02E; B10-B02F; B11-C04; D09-C
TECH
INORGANIC CHEMISTRY - Preferred Material: The stent structure comprises carbon or carbon fiber.
METALLURGY - Preferred Material: The stent structure comprises stainless steel, a nickel-titanium alloy, a cobalt-chromium alloy, or a magnesium alloy.
ORGANIC CHEMISTRY - Preferred Material: The stent structure comprises carbon or carbon fiber.
PHARMACEUTICALS - Preferred Material: The first biologically active compound is rapamycin, heparin, anti-thrombin compounds, prostaglandin

inhibitors, platelet inhibitors, taxol, taxol derivatives, tacrolimus, tachrolimus-containing compounds, cytochalasin, paclitaxel, dexamethasone, a steroid compound, methotrexate, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, tyrosine kinase inhibitors, lidocaine, bupivacaine, or ropivacaine. The second biologically active compound is a growth factor. The growth factor is granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser. sup. 17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO), stem cell factor (SCF), interleukins 1-16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), fit3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, **thyroxine**, or sphingosine 1-phosphate.

POLYMERS - Preferred Material: The stent structure comprises a polymer. The first, second and third layers are polymers. The polymer is poly(ethers), poly(ethylene oxide), poly(ethylene glycol), poly(tetramethylene oxide); vinyl polymers, poly(acrylates), poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic acids, methacrylic acids, poly(vinyl alcohol), poly(vinyl pyrolidone), poly(vinyl acetate); poly(urethanes); cellulose and its derivatives s alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, cellulose acetates; poly(siloxanes); plasticized nylon, plasticized soft nylon, natural rubber, silicone, medical grade silicone rubbers, ethylene-propylene rubber, silicone-carbonate copolymers, poly(olefins, poly(vinyl-olefins), poly(styrene), poly(halo-olefins), poly(isobutylene), polylactide, polylactideco-glycolide, polydioxanone, thermoplastic elastomers, thermoplastics, expanded PTFE, poly(vinyl-chloride), poly(isoprene), poly(isobutylene), poly(butadiene), polymaleic acid, polyamino acids, polyacrylic acids, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohols, hydrophilic polyurethanes, albumin, collagen, **gelatin**, starch, cellulose, dextran, polymaleic acid, polyamino acids and their co-polymers or lightly cross-linked forms, polysaccharides and their derivatives, sodium alginate, karaya gum, **gelatin**, guar gum, agar, align, carrageenans, pectin, locust bean gums, xanthan, starch-based gums, hydroxyalkyl and ethyl ethers of cellulose, sodium carboxymethylcellulose, poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); and/or poly(carbonates). Third layer comprises ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene block copolymers, butylene-styrene block copolymers, silicone rubber, Silastic, and aliphatic polyesters, and/or their copolymers.

INORGANIC CHEMISTRY - Preferred Material: The stent structure comprises carbon or carbon fiber.

METALLURGY - Preferred Material: The stent structure comprises stainless steel, a nickel-titanium alloy, a cobalt-chromium alloy, or a magnesium alloy.

ORGANIC CHEMISTRY - Preferred Material: The stent structure comprises carbon or carbon fiber.

PHARMACEUTICALS - Preferred Material: The first biologically active

compound is rapamycin, heparin, anti-thrombin compounds, prostaglandin inhibitors, platelet inhibitors, taxol, taxol derivatives, tacrolimus, tachrolimus-containing compounds, cytochalasin, paclitaxel, dexamethasone, a steroid compound, methotrexate, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, mesalamine, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin, tyrosine kinase inhibitors, lidocaine, bupivacaine, or ropivacaine. The second biologically active compound is a growth factor. The growth factor is granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), CSF-1, G-CSF Ser. sup. 17, M-CSF, c-mpl ligand (MGDF or TPO), erythropoietin (EPO), stem cell factor (SCF), interleukins 1-16 (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16), fit3 ligand, human growth hormone, B-cell growth factor, B-cell differentiation factor, eosinophil differentiation factor, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta 1, acidic fibroblast growth factor, osteonectin, angiopoietin 1, angiopoietin 2, insulin-like growth factor, platelet-derived growth factor AA, platelet derived growth factor BB, platelet-derived growth factor AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, **thyroxine**, or sphingosine 1-phosphate.

POLYMERS - Preferred Material: The stent structure comprises a polymer. The first, second and third layers are polymers. The polymer is poly(ethers), poly(ethylene oxide), poly(ethylene glycol), poly(tetramethylene oxide); vinyl polymers, poly(acrylates), poly(methacrylates) such as methyl, ethyl, other alkyl, hydroxyethyl methacrylate, acrylic acids, methacrylic acids, poly(vinyl alcohol), poly(vinyl pyrolidone), poly(vinyl acetate); poly(urethanes); cellulose and its derivatives s alkyl, hydroxyalkyl, ethers, esters, nitrocellulose, cellulose acetates; poly(siloxanes); plasticized nylon, plasticized soft nylon, natural rubber, silicone, medical grade silicone rubbers, ethylene-propylene rubber, silicone-carbonate copolymers, poly(olefins, poly(vinyl-olefins), poly(styrene), poly(halo-olefins), poly(isobutylene), polylactide, polylactideco-glycolide, polydioxanone, thermoplastic elastomers, thermoplastics, expanded PTFE, poly(vinyl-chloride), poly(isoprene), poly(isobutylene), poly(butadiene), polymaleic acid, polyamino acids, polyacrylic acids, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohols, hydrophilic polyurethanes, albumin, collagen, **gelatin**, starch, cellulose, dextran, polymaleic acid, polyamino acids and their co-polymers or lightly cross-linked forms, polysaccharides and their derivatives, sodium alginate, karaya gum, **gelatin**, guar gum, agar, align, carrageenans, pectin, locust bean gums, xanthan, starch-based gums, hydroxyalkyl and ethyl ethers of cellulose, sodium carboxymethylcellulose, poly(amides) such as poly(amino acids) and poly(peptides); poly(esters) such as poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and poly(caprolactone); poly(anhydrides); poly(orthoesters); and/or poly(carbonates). Third layer comprises ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene block copolymers, butylene-styrene block copolymers, silicone rubber, Silastic, and aliphatic polyesters, and/or their copolymers.

IT UPIT 20051223

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CMC UPB 20051223

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1867-U

DCR: 104616-U **108879-U** 110156-U 134012-U 147029-U 156376-U
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M1 *02* M423 M424 M740 M781 N103 Q262 M905
DCN: RA0C4V-K RA0C4V-U
DCR: 160852-K 160852-U

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DCN: RA09LI-K RA09LI-U RA0O3V-K RA0O3V-U
DCR: 232204-K 232204-U 91489-K 91489-U

M1 *04* M423 M424 M740 M781 N103 Q262 M905
DCN: RA0DNM-K RA0DNM-U RA0KDA-K RA0KDA-U
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DCN: RA0DIZ-K RA0DIZ-U
DCR: 91496-K 91496-U

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DCN: RA02UP-K RA02UP-U
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DCN: RA0QMT-K RA0QMT-U
DCR: 114760-K 114760-U

M1 *08* M423 M424 M740 M781 N103 Q262 M905 M904
DCN: R16255-K R16255-U RA01ZP-K RA01ZP-U
DCR: 134017-K 134017-U 97925-K 97925-U

M1 *09* M423 M424 M740 M781 N103 Q262 M905
DCN: RA04TA-K RA04TA-U
DCR: 97947-K 97947-U

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DCN: RA04J4-K RA04J4-U
DCR: 97951-K 97951-U

M1 *11* M423 M424 M740 M781 N103 Q262 M905 M904
DCN: RA03SC-K RA03SC-U
DCR: 97954-K 97954-U

M1 *12* M423 M424 M740 M781 N103 Q262 M905
DCN: RA04OE-K RA04OE-U
DCR: 97957-K 97957-U

M1 *13* M423 M424 M740 M781 N103 Q262 M905
DCN: RA01IL-K RA01IL-U
DCR: 97959-K 97959-U

M1 *14* F011 F012 F013 F014 F015 F019 F423 F653 G012 G100 H2 H212 H6
H603 H641 J5 J522 K0 K6 K640 L9 L930 M1 M113 M210 M211 M240 M281
M320 M413 M423 M424 M510 M522 M531 M540 M740 M781 N103 Q262
M905 M904
DCN: RA1WOC-K RA1WOC-U

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          DCR: 97961-K 97961-U
M1 *16*   M423 M424 M740 M781 N103 Q262  M905
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          DCR: 196443-K 196443-U
M1 *17*   F011 F012 F013 F014 F015 F019 F423 F431 G010 G100 H2 H211 J5
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          DCR: 145573-K 145573-U
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          H641 J5 J522 L9 L930 L943 M1 M113 M210 M211 M240 M281 M320 M413
          M423 M424 M510 M522 M531 M540 M740 M781 N103 Q262  M905 M904
          DCN: RA1WOD-K RA1WOD-U
          DCR: 145574-K 145574-U
M1 *19*   M423 M424 M740 M781 N103 Q262  M905
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          DCR: 97942-K 97942-U
M1 *20*   M423 M424 M740 M781 N103 Q262  M905 M904
          DCN: RA04OD-K RA04OD-U
          DCR: 111285-K 111285-U
M1 *21*   M423 M424 M740 M781 N103 Q262  M905
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          DCR: 485836-K 485836-U
M1 *22*   F011 F012 F013 F015 F423 G012 G100 H2 H211 H6 H603 H641 J5 J522
          K0 K6 K640 L9 L930 M1 M113 M280 M320 M413 M423 M424 M510 M521
          M531 M540 M740 M781 N103 Q262  M905 M904
          DCN: RA8A3D-K RA8A3D-U
          DCR: 145575-K 145575-U
M1 *23*   M423 M424 M740 M781 N103 Q262  M905 M904
          DCN: RA00F4-K RA00F4-U
          DCR: 107436-K 107436-U
M1 *24*   M423 M424 M740 M781 N103 Q262  M905
          DCN: RA03RK-K RA03RK-U
          DCR: 123286-K 123286-U
M1 *25*   M423 M424 M740 M781 N103 Q262  M905 M904
          DCN: RA04QH-K RA04QH-U
          DCR: 95150-K 95150-U
M1 *26*   M423 M424 M740 M781 N103 Q262  M905
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          DCR: 453575-K 453575-U
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          DCR: 467512-K 467512-U
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          DCR: 114243-K 114243-U
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          DCN: RA05ZK-K RA05ZK-U
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DCR: 111894-K 111894-U
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DCN: RA63XA-K RA63XA-U
DCR: 231761-K 231761-U
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DCN: RA2DVG-K RA2DVG-U
DCR: 287189-K 287189-U
M1 *35* M423 M424 M740 M781 N103 Q262 M905
DCN: RABUXE-K RABUXE-U
DCR: 753931-K 753931-U
M1 *36* M423 M424 M740 M781 N103 Q262 M905 M904
DCN: RA11A9-K RA11A9-U
DCR: 107411-K 107411-U
M1 *37* M423 M424 M740 M781 N103 Q262 M905
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DCR: 127064-K 127064-U
M1 *38* M423 M424 M740 M781 N103 Q262 M905
DCN: RABNN0-K RABNN0-U
DCR: 775985-K 775985-U
M1 *39* M423 M424 M740 M781 N103 Q262 M905 M904
DCN: RA11ZO-K RA11ZO-U
DCR: 114565-K 114565-U
M1 *40* M423 M424 M740 M781 N103 Q262 M905
DCN: RA0B7G-K RA0B7G-U
DCR: 155378-K 155378-U
M1 *41* M423 M424 M740 M781 N103 Q262 M905
DCN: RAFHY5-K RAFHY5-U
DCR: 278638-K 278638-U
M1 *42* M423 M424 M740 M781 N103 Q262 M905
DCN: RACFB0-K RACFB0-U
DCR: 813364-K 813364-U
M1 *43* M423 M424 M740 M781 N103 Q262 M905
DCN: RA1S8U-K RA1S8U-U
DCR: 285743-K 285743-U
M1 *44* C316 J0 J011 J111 K0 K3 K340 K4 K421 M423 M424 M740 M781 N103 Q262 M905 M904 M910
DCN: R01867-K R01867-U R17645-K R17645-U
DCR: 134012-U 96796-K 96796-U 96799-U
M2 *45* H1 H102 H182 J0 J014 J1 J173 M280 M311 M312 M321 M322 M332 M342 M343 M349 M381 M393 M416 M424 M620 M740 M781 N103 Q262 M905 M904
DCN: R13080-K R13080-U R13081-K R13081-U
DCR: 87437-K 87437-U
M2 *46* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M424 M510 M520 M532 M540 M740 M781 N103 Q262 M905 M904 M910
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DCR: **108879-K 108879-U**
M2 *47* D021 D024 D025 D026 D030 D220 G010 G019 G100 H4 H403 H462 H481 H8 J0 J014 J2 J221 J231 J262 J3 J331 J5 J561 M1 M123 M136 M210 M211 M240 M262 M282 M283 M312 M321 M332 M344 M349 M371 M391 M412 M424 M511 M520 M533 M540 M740 M781 N103 Q262 M905 M904
RIN: 68515
DCN: R18653-K R18653-U
DCR: 103128-K 103128-U
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          DCR: 108275-K 108275-U
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          RIN: 50019
          DCN: R16611-K R16611-U
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M2 *50*   D012 D013 D940 G013 G100 H1 H101 H103 H122 H141 J0 J013 J1 J172
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          DCR: 60080-K 60080-U
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          M510 M521 M532 M540 M740 M781 N103 Q262  M905 M904
          DCN: R12996-K R12996-U
          DCR: 108041-K 108041-U
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          DCR: 100525-K 100525-U
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          DCN: R00165-K R00165-U R14958-K R14958-U
          DCR: 9091-K 9091-U
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          DCR: 91104-K 91104-U
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          H421 H461 H5 H541 H8 J0 J013 J2 J211 J251 J261 M1 M116 M210 M211
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          RIN: 11065 13275
          DCN: R04079-K R04079-U R17068-K R17068-U
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          M424 M511 M521 M530 M540 M740 M781 N103 Q262  M905 M904
          RIN: 40014
          DCN: RA0L63-K RA0L63-U
          DCR: 116277-K 116277-U
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M2 *59*   F011 F012 F433 G014 G100 H1 H181 H2 H201 J0 J011 J3 J311 M1 M123
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DCN: R07915-K R07915-U R16687-K R16687-U
DCR: 89506-K 89506-U
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DCN: R19211-K R19211-U
DCR: 106017-K 106017-U
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DCN: RA0NPZ-K RA0NPZ-U
DCR: 164320-K 164320-U
M5 *62* M424 M740 M781 N103 Q262 M905 M904 M910
DCN: R00002-K R00002-U R14648-K R14648-U
DCR: 92784-K 92784-U 92790-U
M5 *63* M424 M740 M781 N103 Q262 M905 M904 M910
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DCR: 104616-K 104616-U
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DCR: 91637-K 91637-U
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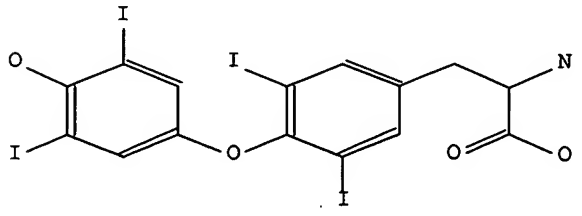
RIN: 05595
DCN: R06391-K R06391-U
DCR: 89459-K 89459-U
M6 *01* Q262 R120 R150 R220 R430 R501 M905
DRN 0002-U 0010-U 0012-U **0050-U** 0125-U 0165-U 0180-U 1117-U 1867-U
M2 *46* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M424 M510 M520 M532 M540 M740 M781 N103 Q262 M905 M904 M910
DCN: **R00050-K R00050-U R04769-K R04769-U**
DCR: **108879-K 108879-U**
AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 17 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-736465 [76] WPIX
CROSS REFERENCE: 2006-038440
DOC. NO. CPI: C2005-224858 [76]

TITLE: Novel polymeric prodrug molecule, useful for covalent conjugation with biological molecule and linkage with carrier, in drug delivery
DERWENT CLASS: A96; B05
INVENTOR: HERSEL U; RAU H; SCHNEPF R; VETTER D; WEGGE T
PATENT ASSIGNEE: (COMP-N) COMPLEX BIOSYSTEMS GMBH
COUNTRY COUNT: 32

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1579873	A1	20050928	(200576)*	EN	52[42]	A61K047-48

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1579873 A1		EP 2004-75892	20040323

PRIORITY APPLN. INFO: EP 2004-75892 20040323
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0047-48 [I,A]; A61K0047-48 [I,C]
BASIC ABSTRACT:

EP 1579873 A1 UPAB: 20060125
NOVELTY - A polymeric prodrug molecule (I), is new.
DETAILED DESCRIPTION - A polymeric prodrug molecule (A1) of formula (I),
T=D or A;
D=residue of amine containing biological molecule; A=leaving group;
X=spacer moiety such as R5-Y6; Y1,Y2=O, S or NR6;
Y3,Y5=O or S;
Y4=O, NR6 or -C(R7)(R8)-;
Y6=O, S, NR6, succinimide, maleimide, unsaturated carbon-carbon bonds or any heteroatom containing a free electron pair; R3=H, (un)substituted alkyl or heteroalkyl, aryls, substituted aryl, (un)substituted heteroaryls, cyano, nitro, halogen, carboxy, carboxyalkyl, alkylcarbonyl, or carboxamidoalkyl;
R4=H, (un)substituted alkyl or heteroalkyl, aryl, substituted aryl, (un)substituted heteroaryl, alkoxy or heteroalkyloxy, aryloxy, or heteroaryloxy;
R5=(un)substituted alkyl or heteroalkyl, aryls, substituted aryls, (un)substituted heteroaryls, carboxyalkyl, alkylcarbonyl or carboxamidoalkyl;
R7,R8=H, (un)substituted alkyl or heteroalkyl, aryls, substituted aryls, (un)substituted heteroaryls, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, cyano, or halogen; R6=H, (un)substituted alkyl or heteroalkyl, aryls, substituted aryls, (un)substituted heteroaryls; R1=polymer;
R2=H, (un)substituted alkyl or cycloalkyl, aryl, substituted aryl, (un)substituted heteroalkyl, (un)substituted heteroaryl, (un)substituted alkoxy, (un)substituted heteroalkyloxy, aryloxy, heteroaryloxycyano, carboxy, carboxyalkyl, alkylcarbonyl, carboxamidoalkyl, or peptide sequences which can be cleaved by specific enzymes; n=zero or positive integer; and Ar=multi-substituted aromatic hydrocarbon or aromatic heterocycle. INDEPENDENT CLAIMS are also included for the following: (i) synthesizing (M1) A1, involves providing a starting molecule of formula (II), synthesizing at least one intermediate compound from the starting molecule of formula (II), and attaching an amine-containing a biological molecule to at least one intermediate compound; (ii) hydrolyzing (M2) A1, involves placing A1 in solution with a pH of approximately 7.4;
(iii) administrating (M3) a biological compound to a living organism, involves attaching an amine-containing compound through an amino group to a carrier molecule by means of a linker, administering the amine-containing compound and

the carrier molecule to the living organism, and cleaving the amine-containing compound from the carrier molecule by means of a substantially non-enzymatic reaction; and (iv) cleaving (M4) the amine-containing compound from the carrier by a substantially non-enzymatic reaction of the linker, where the amine-containing compound is attached to a carrier by a linker.
Y2,Y3,X,R3,R4,Ar=same as defined above.
USE - A1 is useful for covalent conjugation with a biological active molecule and linkage with a carrier, where in A1, R1 is a protecting group PG1 and T is a leaving group. The biological active molecule is an amine-containing molecule, preferably peptide, polypeptide or protein (claimed). A1 is useful in therapeutic applications for drug delivery.
ADVANTAGE - A1 has reversible linkages to amino groups of biologically active entities such as peptides, proteins, natural products or synthetic chemical compounds. A1 can be administered without concomitant side effects and risk of over dosing. Release of drug occurs over time, thus reducing the necessity of repeated and frequent administration of the drug.
DESCRIPTION OF DRAWINGS - The figure shows the diagram of the carrier-linked prodrug.

MANUAL CODE: CPI: A10-E01; A12-V01; B02-Z; B04-C01; B04-C02; B04-C03B; B04-C03C; B04-C03D; B04-G01; B04-H01; B04-H02; B04-H04; B04-H05; B04-H06; B04-H07; B04-H08; B04-H14; B04-H15; B04-H17; B04-H19; B04-J01; B04-J04A; B04-J05; B04-J07; B04-J08; B04-J09; B04-J10; B04-J11; B04-L01; B04-L03; B04-L05; B04-N01; B04-N02; B06-D01; B07-D03; B07-D05; B07-D12; B07-E01; B09-D01; B10-A10; B10-B01B; B10-B03B; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-F01; B14-F02C; B14-F02D; B14-H01; B14-J01; B14-P01

TECH

BIOTECHNOLOGY - Preferred Method: In (M1), a first one of at least one intermediate compound is an intermediate molecule of formula (III) synthesized by acylating Y2 with formula called (IIIa).
R2,Y1-Y4,R3,R4,Ar=same as defined above; and
PG1=first protecting group or absent.
The second one of the at least one intermediate compound is an intermediate compound of formula (IV) formed by activating the compound of formula (III) with an activating agent,A,Y1-Y5,R2-R4,PG1,X=same as defined above.
The activating agent is chosen from activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate. The amine-containing biological molecule is attached to the compound of formula (IV) by displacement of the leaving group A. (M1) further involves a step of removal of the reversible first protecting group PG1, where the step of removal of the reversible protection group PG1 is carried out using a reagent chosen from reagents consisting of trifluoroacetic acid or dithiothreitol (DTT). (M1) further involves a step of attaching a polymer R1 to X to form a third one of the at least one intermediate compound, having a formula (VI), and a step of activating the third one of the at least one intermediate compound by using an activating agent to form a fourth one of the at least one intermediate compound and having a formula (VII).R1-R4,Y1-Y4,X,Ar=same as defined above.
The amine-containing biological molecule is attached to the compound of formula (VII) by displacement of the leaving group A. (M1) further involves a step of reacting the starting molecule of formula (II) with a first polymer R1 to attach the first polymer R1 to X, a step of protecting Y2 with a second protective group PG2, and a step of activating the molecule with an activating agent and reacting with an amine-containing biological molecule to form a fifth one of the at least one intermediate compound and having formula (X).
R1,R3,R4,Y2,Y3,Y5,X,Ar=same as defined above; and
PG2=PG1.

The second protecting group PG2 is removed from Y2, and Y2 is acylated with formula called (IIIa). The removal of the second reversible group PG2 is carried out using a reagent chosen from reagents consisting of trifluoroacetic acid or DTT. (M1) further involves a step of attaching a removable first protecting group PG1 to X and a removable second protecting group PG2 to the starting compound of formula (II) and thereafter activation using an activating agent to form a sixth one of the at least one intermediate compound and having formula (VIII), and a step of removing the first protecting group PG1 from X and attaching a polymer R1, where the second protecting group PG2 is removed from Y2, and Y2 is acylated with formula called (IIIa).

R3,R4,Y2,Y3,Y5,X,Ar,PG1=same as defined above; and

PG2=PG1.

The amine-containing biological molecule is attached to the sixth one of the at least one intermediate compound by displacement of the leaving group A. (M1) further involves a step of removing the first protecting group PG1 from X and attaching a polymer R1. In (M2), the solution is an extra-cellular fluid. In (M3), the amine-containing compound is a biological molecule, where the biological molecule is chosen from biological molecules consisting of small molecule biological agents or biopolymers. The biopolymers are chosen from proteins, polypeptides, oligonucleotides and peptide nucleic acids. The polypeptides are chosen from ACTH, adenosine deaminase, agalsidase, albumin, alpha-1 antitrypsin (AAT), alpha-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1alpha, 1beta, 2, 3, 4, 6, 10, 11 or 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alpha2a, alpha2b, alpha2c, beta1a, beta1b, gamma1a or gamma1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), thyroid stimulating hormone (TSH), urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is a protein prepared by recombinant DNA technology. The protein is chosen from antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins. The small molecule biological agents are chosen from central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, and cardiovascular agents with at least one primary or secondary amino group, preferably chosen from daunorubicin, doxorubicin, idarubicin, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxaxin, enoxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamin, dobutamin, lisinopril, serotonin, acivicin and carbutamid. (M3)-(M4) is carried out in an extra-cellular fluid. The substantially

non-enzymatic reaction comprises a step of hydrolysis or intramolecular cyclization. (M3) further involves a step of sterically protecting at least portion of the linker by a sterically demanding carrier. The amine-containing compound is a biological compound.
BIOTECHNOLOGY - Preferred Method: In (M1), a first one of at least one intermediate compound is an intermediate molecule of formula (III) synthesized by acylating Y2 with formula called (IIIa).
R2,Y1-Y4,R3,R4,Ar=same as defined above; and
PG1=first protecting group or absent.
The second one of the at least one intermediate compound is an intermediate compound of formula (IV) formed by activating the compound of formula (III) with an activating agent,A,Y1-Y5,R2-R4,PG1,X=same as defined above.
The activating agent is chosen from activating agents consisting of 4-nitrophenyl chloroformate or disuccinyl carbonate. The amine-containing biological molecule is attached to the compound of formula (IV) by displacement of the leaving group A. (M1) further involves a step of removal of the reversible first protecting group PG1, where the step of removal of the reversible protection group PG1 is carried out using a reagent chosen from reagents consisting of trifluoroacetic acid or dithiothreitol (DTT). (M1) further involves a step of attaching a polymer R1 to X to form a third one of the at least one intermediate compound, having a formula (VI), and a step of activating the third one of the at least one intermediate compound by using an activating agent to form a fourth one of the at least one intermediate compound and having a formula (VII).R1-R4,Y1-Y4,X,Ar=same as defined above.
The amine-containing biological molecule is attached to the compound of formula (VII) by displacement of the leaving group A. (M1) further involves a step of reacting the starting molecule of formula (II) with a first polymer R1 to attach the first polymer R1 to X, a step of protecting Y2 with a second protective group PG2, and a step of activating the molecule with an activating agent and reacting with an amine-containing biological molecule to form a fifth one of the at least one intermediate compound and having formula (X).
R1,R3,R4,Y2,Y3,Y5,X,Ar=same as defined above; and
PG2=PG1.
The second protecting group PG2 is removed from Y2, and Y2 is acylated with formula called (IIIa). The removal of the second reversible group PG2 is carried out using a reagent chosen from reagents consisting of trifluoroacetic acid or DTT. (M1) further involves a step of attaching a removable first protecting group PG1 to X and a removable second protecting group PG2 to the starting compound of formula (II) and thereafter activation using an activating agent to form a sixth one of the at least one intermediate compound and having formula (VIII), and a step of removing the first protecting group PG1 from X and attaching a polymer R1, where the second protecting group PG2 is removed from Y2, and Y2 is acylated with formula called (IIIa).
R3,R4,Y2,Y3,Y5,X,Ar,PG1=same as defined above; and
PG2=PG1.
The amine-containing biological molecule is attached to the sixth one of the at least one intermediate compound by displacement of the leaving group A. (M1) further involves a step of removing the first protecting group PG1 from X and attaching a polymer R1. In (M2), the solution is an extra-cellular fluid. In (M3), the amine-containing compound is a biological molecule, where the biological molecule is chosen from biological molecules consisting of small molecule biological agents or biopolymers. The biopolymers are chosen from proteins, polypeptides, oligonucleotides and peptide nucleic acids. The polypeptides are chosen from ACTH, adenosine deaminase, agalsidase, albumin, alpha-1 antitrypsin (AAT), alpha-1 proteinase inhibitor (API), alteplase, anistreplase, ancrod

serine protease, antibodies (monoclonal or polyclonal, and fragments or fusions), antithrombin III, antitrypsins, aprotinin, asparaginases, biphalin, bone-morphogenic proteins, calcitonin (salmon), collagenase, DNase, endorphins, enfuvirtide, enkephalins, erythropoietins, factor VIIa, factor IX, fibrinolysin, fusion proteins, follicle-stimulating hormones, granulocyte colony stimulating factor (G-CSF), galactosidase, glucagon, glucocerebrosidase, granulocyte macrophage colony stimulating factor (GM-CSF), phospholipase-activating protein (PLAP), gonadotropin chorionic (hCG), hemoglobins, hepatitis B vaccines, hirudin, hyaluronidases, idurnonidase, immune globulins, influenza vaccines, interleukins (1alpha, 1beta, 2, 3, 4, 6, 10, 11 or 12), IL-1 receptor antagonist (rhIL-1ra), insulins, interferons (alpha2a, alpha2b, alpha2c, beta1a, beta1b, gamma1a or gamma1b), keratinocyte growth factor (KGF), transforming growth factors, lactase, leuprolide, **levothyroxine**, luteinizing hormone, lyme vaccine, natriuretic peptide, pancrelipase, papain, parathyroid hormone, PDGF, pepsin, platelet activating factor acetylhydrolase (PAF-AH), prolactin, protein C, octreotide, secretin, sermorelin, superoxide dismutase (SOD), somatropins (growth hormone), somatostatin, streptokinase, sucrase, tetanus toxin fragment, tilactase, thrombins, thymosin, thyroid stimulating hormone, thyrotropin, tumor necrosis factor (TNF), TNF receptor-IgG Fc, tissue plasminogen activator (tPA), thyroid stimulating hormone (TSH), urate oxidase, urokinase, vaccines, and plant protein such as lectin and ricin. The protein is a protein prepared by recombinant DNA technology. The protein is chosen from antibody fragments, single chain binding proteins, catalytic antibodies and fusion proteins. The small molecule biological agents are chosen from central nervous system-active agents, anti-infective, anti-neoplastic, antibacterial, anti-fungal, analgesic, contraceptive, anti-inflammatory, steroidal, vasodilating, vasoconstricting, and cardiovascular agents with at least one primary or secondary amino group, preferably chosen from daunorubicin, doxorubicin, idarubicin, mitoxantron, aminoglutethimide, amantadine, diaphenylsulfon, ethambutol, sulfadiazin, sulfamerazin, sulfamethoxazol, sulfalen, clinafloxacin, moxifloxacin, ciprofloxaxin, enoxacin, norfloxacin, neomycin B, sprectinomycin, kanamycin A, meropenem, dopamin, dobutamin, lisinopril, serotonin, acivicin and carbutamid. (M3)-(M4) is carried out in an extra-cellular fluid. The substantially non-enzymatic reaction comprises a step of hydrolysis or intramolecular cyclization. (M3) further involves a step of sterically protecting at least portion of the linker by a sterically demanding carrier. The amine-containing compound is a biological compound.

ABEX DEFINITIONS - Preferred Definitions: - biological molecule=small molecule biological agents or biopolymers; - R4=small substituents consisting of H, methyl, ethyl, ethoxy, methoxy or other alkyls, or 1-6C heteroalkyl; - R1=polymers consisting of polyalkyloxy-based polymers like poly(propylene glycol) or poly(ethylene glycol), dextran, chitosan, hyaluronic acid and derivatives, alginate, agarose, cellulose, hydroxyethyl starch and other carbohydrate-based polymers, poly(vinyl alcohols), poly(oxazolines), poly(anhydrides), poly(ortho esters), poly(carbonates), poly(urethanes), poly(acrylic acids), poly(acrylamides) such as hydroxypropylmethacrylamide, poly(organophosphazenes), poly(vinylpyrrolidone), poly(cyanoacrylates), poly(esters) such as poly(lactic acid) or poly(glycolic acids), poly(iminocarbonates), poly(amino acids) such as poly(glutamic acid), collagen, gelatin, copolymers, grafted copolymers, cross- linked polymers, or block copolymers from the above listed polymers, preferably branched or hyperbranched polymer, dendrimer or dense star polymer, or biopolymer being cross-linked polymer, more preferably protein, most preferably albumin, antibody, fibrin, casein or any other plasma protein, in which R1 further includes one or more biological substances, and the polymer of R1 has at least one functional group for linkage to X; - functional

group=carboxylic acid and activated derivatives, amino, maleimide, thiol, sulfonic acid and derivatives, carbonate and derivatives, carbamate and derivatives, hydroxyl, aldehyde, ketone, hydrazine, isocyanate, isothiocyanate, phosphoric acid and derivatives, phosphonic acid and derivatives, haloacetyl, alkyl halides, acryloyl, arylating agents like aryl fluorides, hydroxylamine, disulfides like pyridyl disulfide, vinyl sulfone, vinyl ketone, diazoalkanes, diazoacetyl compounds, epoxide, oxirane or aziridine, preferably thiol, maleimide, amino, carboxylic acid and derivatives, carbonate and derivatives, carbamate and derivatives, aldehyde and haloacetyl; - A=leaving groups consisting of chloride, nitrophenoxy, imidazolyl, N-hydroxysuccinimidyl, N-hydroxybenzotriazolyl, N-hydroxyazobenzotriazolyl, pentafluorphenoxy or N-hydroxysulfosuccinimidyl; - moiety=formula (1), preferably chosen from formulae (1a)-(1c), most preferably (1b) or (1c); - R2=(un)substituted non-toxic alkyl or heteroalkyl, containing preferably a nucleophile that can perform a nucleophilic attack at the carbonyl carbon and thus catalyse the cleavage of a masking group by intramolecular catalysis or cyclization; - R7, R8=not hydrogen; - Ar=one of formulae (2a)-(2r), e.g., (2a)-(2d);and - W'=O, S or N.

EXAMPLE - Compound such as rh-insulin (80 mg (13.8 muM)) were dissolved in 4 ml 1/1 (v/v) dimethylformamide (DMF)/dimethylsulfoxide (DMSO) and 40 mul diisopropylethylamine (DIEA) was added. Then, 8 mg (17 muM) 5-(and-6)-carboxyfluorescein succinimidyl ester was added and the solution was stirred for 30 minutes at room temperature. The 4 ml 5/5/1 (v/v/v) acetonitirle/water/acetic acid were added, product N(epsilonB29)-fluorescein insulin was purified by reverse phase-HPLC and lyophilized. Then, N(epsilonB29)-fluorescein insulin in 1/1 (v/v) DMF/DMSO was mixed with a solution of 0.9 eq carbonate of formula 7a in DMSO. The resulting solutions were adjusted to basic pH with DIEA and stirred for 3 hours at room temperature. RP-HPLC purification gave Mmt-protected intermediates. After lyophilization, the intermediates were dissolved in 95/5 (v/v) trifluoroacetic acid (TFA)/triethylsilane and stirred for 5 minutes. Volatiles were removed under nitrogen flow, to obtain N(epsilonB29)-fluorescein-N(alphaA1)-linker-insulin, which was purified by RP-HPLC.

IT UPIT 20060125

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H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321
M332 M343 M349 M371 M391 M411 M423 M431 M510 M520 M532 M540 M630
M710 M720 M782 N153 N209 N261 N262 N263 N309 N331 N332 N341 N352
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RA11AM-Q
DCR: **99369-M 99369-N 99369-P**
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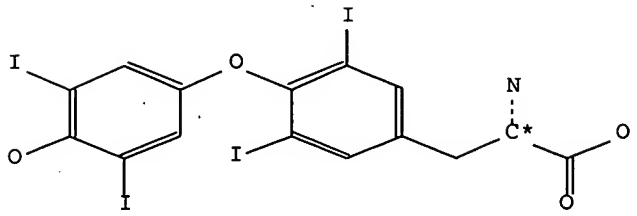
AN.S DCR-99369

CN.P LEVOTHYROXINE SODIUM
CN.S 2-amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionate; Sodium
SDCN RA11AM

CM 1

Na

CM 2



L86 ANSWER 18 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-375494 [35] WPIX
DOC. NO. CPI: C2004-141131 [35]
TITLE: Glutamine supplementation for humans, useful for treating patients suffering from e.g. short bowel syndrome, burns, bone marrow transplant, oral mucositis, cancer and Crohn's disease, comprises oral administration of N-acetyl L-glutamine
DERWENT CLASS: A96; B05; D13
INVENTOR: BAXTER J; BAXTER J H; LOPEZ J M; RUEDA R
PATENT ASSIGNEE: (ABBO-C) ABBOTT LAB
COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2004032653	A1	20040422	(200435)*	EN	72 [11]	
AU 2002356547	A1	20040504	(200465)	EN		
EP 1555896	A1	20050727	(200549)	EN		
BR 2002015904	A	20050809	(200554)	PT		
IN 2005000269	P3	20050930	(200579)	EN		A23L001-304
MX 2005003732	A1	20051001	(200620)	ES		
JP 2006515832	W	20060608	(200638)	JA	50	
CN 1717184	A	20060104	(200639)	ZH		A23L001-304
KR 2005071562	A	20050707	(200643)	KO		A61K031-195
ZA 2005002843	A	20061025	(200674)	EN	78	A23L000-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004032653	A1	WO 2002-US32172	20021008

AU 2002356547 A1	AU 2002-356547 20021008
BR 2002015904 A	BR 2002-15904 20021008
CN 1717184 A	CN 2002-829976 20021008
EP 1555896 A1	EP 2002-807988 20021008
EP 1555896 A1	WO 2002-US32172 20021008
BR 2002015904 A	WO 2002-US32172 20021008
IN 2005000269 P3	WO 2002-US32172 20021008
MX 2005003732 A1	WO 2002-US32172 20021008
JP 2006515832 W	WO 2002-US32172 20021008
KR 2005071562 A	WO 2002-US32172 20021008
JP 2006515832 W	JP 2004-542984 20021008
MX 2005003732 A1	MX 2005-3732 20050407
KR 2005071562 A	KR 2005-706141 20050408
IN 2005000269 P3	IN 2005-MN269 20050411
ZA 2005002843 A	ZA 2005-2843 20050407

FILING DETAILS:

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AU 2002356547	A1	Based on	WO 2004032653	A
EP 1555896	A1	Based on	WO 2004032653	A
BR 2002015904	A	Based on	WO 2004032653	A
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KR 2005071562	A	Based on	WO 2004032653	A

PRIORITY APPLN. INFO: US 2002-973105 20021008
INT. PATENT CLASSIF.:
MAIN: A23L; A23L001-304; A61K031-195
SECONDARY: A61K
IPC ORIGINAL: A23L0001-304 [I,A]; A23L0001-304 [I,C]; A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0031-7016 [I,A]; A61K0031-715 [I,A]; A61K0033-14 [I,A]; A61K0038-00 [I,A]; A61P0003-00 [I,C]; A61P0003-02 [I,A]
IPC RECLASSIF.: A23L0001-29 [I,A]; A23L0001-29 [I,C]; A23L0001-304 [I,A]; A23L0001-304 [I,C]; A23L0001-305 [I,A]; A23L0001-305 [I,C]; A61K0031-185 [I,C]; A61K0031-195 [I,A]

BASIC ABSTRACT:

WO 2004032653 A1 UPAB: 20060203

NOVELTY - Glutamine supplementation to a human comprises oral administration of N-acetyl L-glutamine (I) or its nutritionally acceptable salt.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) an aqueous solution comprising 30-95 mEq of sodium per liter, 10-30 mEq of potassium per liter, 10-40 mEq of citrate per liter, less than 3.0 weight/weight% of one carbohydrate and at least 5 mmoles (I) or its nutritionally equivalent salt per liter of solution; (2) a liquid nutritional formula comprising 8-35 % protein component, 36-76 % carbohydrate component, 6-51 % lipid component and 1-23 % on a caloric basis of the protein component in the form of (I); (3) an adult liquid nutritional formula comprising 14-35 % protein component, 36-76 % carbohydrate component, 6-51 % lipid component and at least 35 mmoles of (I) per 1000 kcal of nutritional formula; and (4) a liquid nutritional formula for a non-adult patient comprising 8-25 % protein component, 39-44 % carbohydrate component, 45-51 % lipid component and at least 5.0 mmoles of (I) per 1000 kcal of nutritional formula.

ACTIVITY - Antiinflammatory; Gastrointestinal-Gen.; Vulnerary; Immunosuppressive; Cytostatic; Antimicrobial; Anti-HIV.

MECHANISM OF ACTION - None given in the source material.

USE - (A) Is used as supplement for human suffering from gastrointestinal surgery, gastrointestinal resection, small bowel transplant, post surgical

trauma, starvation, critical illnesses and injuries, multiple trauma, short bowel syndrome, burns, bone marrow transplant, AIDS, oral mucositis, cancer, Celiac disease, Crohn's disease, necrotizing enterocolitis, prematurity of the gut, infections of opportunity, gut deterioration associated with particular treatments and/or restricted oral feeding. (A) and the liquid nutritional formula is used to decrease intestinal mucosal inflammation in patients suffering from Celiac Disease (all claimed).

ADVANTAGE - The compositions possess long-term stability and provide the N-acetyl-L-glutamine in a form that is bioavailable for humans. The glutamine and N-acetyl-L-glutamine unavailability studies were conducted to determine the proportion of bioavailable N-acetyl-L-glutamine in comparison to glutamine in pig models. The results showed that the N-acetyl-L-glutamine was absorbed mainly in the duodenum and upper jejunum, where at least 77% of the dose was adsorbed. MANUAL CODE: CPI: A12-V01; B04-B01B; B04-B01C1; B04-B01C2; B04-C02B2; B04-N01; B04-N02; B05-A01A; B05-A01B; B05-A03A; B05-B01P; B05-C04; B05-C07; B05-C08; B06-D01; B07-A02; B07-D03; B07-D09; B10-A07; B10-A17; B10-B01B; B10-B02; B10-B02B; B10-C02; B10-C04E; B14-E10C; B14-E11; B14-G02D; D03-H01T

TECH

PHARMACEUTICALS - Preferred Components: The nutritionally acceptable salt is lithium, sodium (preferably sodium chloride, sodium citrate, sodium bicarbonate, sodium carbonate and/or sodium hydroxide), potassium (present in the quantity of 10-30 mEq/l, preferably potassium citrate, potassium chloride, potassium bicarbonate, potassium carbonate, and/or potassium hydroxide), calcium, magnesium or aluminum, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine and/or piperazine.

The lipid component in liquid nutritional formula is coconut oil, soy oil, corn oil, olive oil, safflower oil, high oleic safflower oil, MCT oil (medium chain triglycerides), sunflower oil, high oleic sunflower oil, palm oil, palm olein, canola oil, fish oil, palm kernel oil, menhaden oil, soybean oil, cottonseed oil, lecithin, lipid sources of arachidonic acid and docosahexaneoic acid and/or structured lipids.

The protein component in the liquid nutritional formula comprises intact protein is soy based protein, milk based protein, casein protein, whey protein, rice protein, beef collagen, pea protein and/or potato protein (preferably free amino acids selected from the group consisting of tryptophan, tyrosine, cyst(e)ine, methionine, arginine, leucine, valine, lysine, phenylalanine, isoleucine, threonine, histidine, carnitine, taurine, glycine, alanine, serine, cystine, **thyroxine** aspartic acid, asparagine, glutamic acid glutamine hydroxylysine, proline and/or hydroxyproline).

The carbohydrate component in the liquid nutritional formula is hydrolyzed, intact, natural and chemically modified starches sourced from corn, tapioca, rice or potato in waxy or non-waxy forms, sugars such as glucose, fructose, lactose, sucrose, maltose, high fructose corn syrup and/or corn syrup solids.

Preferred Composition: The aqueous solution comprises 20-300 (preferably 25-200) mmoles of (I) or its nutritionally equivalent salt per liter of solution and the aqueous solution further contains 30-80 mEq/l chloride (preferably potassium chloride, sodium chloride and zinc chloride), at least one flavor, at least one artificial sweetener, at least one gelling agent (agar, alginic acid and salts, gum arabic, gum acacia, gum talha, cellulose derivatives, curdlan, fermentation gums, furcellaran, **gelatin**, gellan gum, gum ghatti, guar gum, iota carrageenan, irish moss, kappa carrageenan, konjac flour, gum karaya, lambda carrageenan,

larch gum/arabinogalactan, locust bean gum, pectin, tamarind seed gum, quantity sufficient to support a self supporting three dimensional structure), rice flour and a indigestible oligosaccharide.
In the aqueous solution, the carbohydrate is a mixture of dextrose and fructose, present in a quantity of less than 3 wt/wt% (preferably 30-95 mEq/l) and 20-40 mEq/l citrate (potassium citrate, sodium citrate and citric acid) is present.
The nutritional formula comprises 35-160 mmoles (preferably 5-32 mmoles) of (I) or its nutritionally acceptable salt per 1000 kcal of nutritional formula.
The liquid nutritional formula contains less than 1.0 g of pyroglutamic acid per 1500 kcal of formula.
The liquid nutritional formula is an adult formula and it contains 14-35 % protein component, 36-76 % carbohydrate component, 6-41 % lipid component and (I) or its nutritionally acceptable salt comprises 1-25 % on a caloric basis of the protein calories.
The liquid nutritional formula is for non-adults and it contains 8-25 % protein component, 39-44 % carbohydrate component, 45-51 % lipid component and (I) or its nutritionally acceptable salt comprises 1-12 % on a caloric basis of the protein calories.
The liquid nutritional formula further comprises vitamins and minerals (calcium, phosphorus, sodium, chloride, magnesium, manganese, iron, copper, zinc, selenium, iodine, chromium, molybdenum, m-inositol, carnitine, taurine, Vitamins A, C, D, E, K and/or the B complex.
PHARMACEUTICALS - Preferred Components: The nutritionally acceptable salt is lithium, sodium (preferably sodium chloride, sodium citrate, sodium bicarbonate, sodium carbonate and/or sodium hydroxide), potassium (present in the quantity of 10-30 mEq/l, preferably potassium citrate, potassium chloride, potassium bicarbonate, potassium carbonate, and/or potassium hydroxide), calcium, magnesium or aluminum, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephenamine, N,N'-dibenzylethylenediamine, ethylenediamine, ethanolamine, diethanolamine, piperidine and/or piperazine.
The lipid component in liquid nutritional formula is coconut oil, soy oil, corn oil, olive oil, safflower oil, high oleic safflower oil, MCT oil (medium chain triglycerides), sunflower oil, high oleic sunflower oil, palm oil, palm olein, canola oil, fish oil, palm kernel oil, menhaden oil, soybean oil, cottonseed oil, lecithin, lipid sources of arachidonic acid and docosahexaneoic acid and/or structured lipids.
The protein component in the liquid nutritional formula comprises intact protein is soy based protein, milk based protein, casein protein, whey protein, rice protein, beef collagen, pea protein and/or potato protein (preferably free amino acids selected from the group consisting of tryptophan, tyrosine, cyst(e)ine, methionine, arginine, leucine, valine, lysine, phenylalanine, isoleucine, threonine, histidine, carnitine, taurine, glycine, alanine, serine, cystine, **thyroxine** aspartic acid, asparagine, glutamic acid glutamine hydroxylysine, proline and/or hydroxyproline).
The carbohydrate component in the liquid nutritional formula is hydrolyzed, intact, natural and chemically modified starches sourced from corn, tapioca, rice or potato in waxy or non-waxy forms, sugars such as glucose, fructose, lactose, sucrose, maltose, high fructose corn syrup and/or corn syrup solids.
Preferred Composition: The aqueous solution comprises 20-300 (preferably 25-200) mmoles of (I) or its nutritionally equivalent salt per liter of solution and the aqueous solution further contains 30-80 mEq/l chloride (preferably potassium chloride, sodium chloride and zinc chloride), at

least one flavor, at least one artificial sweetener, at least one gelling agent (agar, alginic acid and salts, gum arabic, gum acacia, gum talha, cellulose derivatives, curdlan, fermentation gums, furcellaran, **gelatin**, gellan gum, gum ghatti, guar gum, iota carrageenan, irish moss, kappa carrageenan, konjac flour, gum karaya, lambda carrageenan, larch gum/arabinogalactan, locust bean gum, pectin, tamarind seed gum, quantity sufficient to support a self supporting three dimensional structure), rice flour and a indigestible oligosaccharide.

In the aqueous solution, the carbohydrate is a mixture of dextrose and fructose, present in a quantity of less than 3 wt/wt% (preferably 30-95 mEq/l) and 20-40 mEq/l citrate (potassium citrate, sodium citrate and citric acid) is present.

The nutritional formula comprises 35-160 mmoles (preferably 5-32 mmoles) of (I) or its nutritionally acceptable salt per 1000 kcal of nutritional formula.

The liquid nutritional formula contains less than 1.0 g of pyroglutamic acid per 1500 kcal of formula.

The liquid nutritional formula is an adult formula and it contains 14-35 % protein component, 36-76 % carbohydrate component, 6-41 % lipid component and (I) or its nutritionally acceptable salt comprises 1-25 % on a caloric basis of the protein calories.

The liquid nutritional formula is for non-adults and it contains 8-25 % protein component, 39-44 % carbohydrate component, 45-51 % lipid component and (I) or its nutritionally acceptable salt comprises 1-12 % on a caloric basis of the protein calories.

The liquid nutritional formula further comprises vitamins and minerals (calcium, phosphorus, sodium, chloride, magnesium, manganese, iron, copper, zinc, selenium, iodine, chromium, molybdenum, m-inositol, carnitine, taurine, Vitamins A, C, D, E, K and/or the B complex.

IT UPIT 20060203
107779-CL; 200757-CL; 90158-CL; 290162-CL; 107463-CL; 184616-CL; 184599-CL; 91613-CL; 102715-CL; 106388-CL; 108125-CL; 114557-CL; 114054-CL; 95167-CL; 91442-CL; 150656-CL; 107462-CL; 91676-CL; 184614-CL; 91481-CL; 159573-CL; 196509-CL; 79488-CL; 2853-CL; 100051-CL; 127-CL; 114-CL; 110843-CL; 130597-CL; 37837-CL; 303-CL; 104520-CL; 3589-CL; 104516-CL; 68-CL; 104530-CL; 107317-CL; 107324-CL; 2-CL; 97308-CL; **108879-CL**; 129496-CL; 6144-CL; 129495-CL; 8188-CL; 129499-CL; 2634-CL; 86970-CL; 129502-CL; 99222-CL; 191493-CL; 849-CL; 107360-CL; 104541-CL; 129510-CL; 129498-CL; 8181-CL; 8187-CL; 8184-CL; 129497-CL; 129500-CL; 129481-CL; 90095-CL; 73384-CL; 2006-CL; 8189-CL; 8182-CL; 92130-CL; 8186-CL

CMC UPB 20060203
DRN: 0038-U **0050-U** 0080-U 0104-U 0115-U 0116-U 0117-U 0135-U 0187-U 0241-U 0243-U 0292-U 0300-U 0312-U 0419-U 0480-U 0671-U 0828-U 1151-U 1202-U 1210-U 1221-U 1258-U 1287-U 1372-U 1383-U 1391-U 1409-U 1512-U 1514-U 1628-U 1636-U 1654-U 1655-U 1661-U 1678-U 1706-U 1833-U 1863-U

DCR: 100051-U 104516-U 104520-U 104530-U 107317-U 107324-U 107779-U **108879-U** 114-U 127-U 129481-U 129495-U 129496-U 129497-U 129498-U 129499-U 129500-U 129502-U 129510-U 129792-U 129991-U 130280-U 130395-U 130928-U 131311-U 132222-U 132384-U 132385-U 132386-U 132388-U 132389-U 132390-U 132391-U 132393-U 132394-U 132396-U 133509-U 133510-U 133604-U 133611-U 133908-U 134498-U 134730-U 138194-U 140723-U 140725-U 141452-U 144395-U 145033-U 147471-U 151402-U 159060-U 188253-U 191428-U 1979-U 2-U 2006-U 21317-U 2140-U 2407-U 2414-U 2466-U 2471-U 250717-U 2634-U 278358-U 278359-U 2853-U 303-U 3589-U 37837-U 42841-U 6129-U 6139-U 6144-U 6146-U 6268-U 6373-U 68-U 68180-U 72864-U 73384-U 7460-U 75192-U 79488-U 8181-U 8182-U 8184-U 8186-U 8187-U 8188-U 8189-U 8193-U 8197-U 8200-U 8214-U 849-U 8682-U 8685-U 86970-U 87079-U 8757-U

92130-U 95073-U 95095-U 98268-U 99222-U 99344-U 99996-U
M1 *01* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01863-K R01863-M R01863-T
DCR: 107779-K 107779-M 107779-T 107779-U
M1 *02* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA00GT-K RA00GT-M RA00GT-T
DCR: 200757-K 200757-M 200757-T 200799-K 200799-M 200799-T
M1 *03* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R24040-K R24040-M R24040-T
DCR: 90158-K 90158-M 90158-T
M1 *04* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA1VD9-K RA1VD9-M RA1VD9-T
DCR: 290162-K 290162-M 290162-T
M1 *05* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA02QQ-K RA02QQ-M RA02QQ-T
DCR: 107463-K 107463-M 107463-T
M1 *06* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA00H3-K RA00H3-M RA00H3-T
DCR: 184616-K 184616-M 184616-T
M1 *07* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA01IK-K RA01IK-M RA01IK-T
DCR: 184599-K 184599-M 184599-T
M1 *08* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA021E-K RA021E-M RA021E-T
DCR: 91613-K 91613-M 91613-T
M1 *09* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA0217-K RA0217-M RA0217-T
DCR: 102715-K 102715-M 102715-T
M1 *10* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA03IT-K RA03IT-M RA03IT-T
DCR: 106388-K 106388-M 106388-T
M1 *11* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA03E1-K RA03E1-M RA03E1-T
DCR: 108125-K 108125-M 108125-T
M1 *12* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA0410-K RA0410-M RA0410-T
DCR: 114557-K 114557-M 114557-T
M1 *13* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA040W-K RA040W-M RA040W-T
DCR: 114054-K 114054-M 114054-T
M1 *14* H7 H723 J0 J011 J1 J171 M226 M231 M262 M281 M320 M416 M423 M431
M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: RA07ZC-K RA07ZC-M RA07ZC-T
DCR: 95167-K 95167-M 95167-T
M1 *15* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA0146-K RA0146-M RA0146-T
DCR: 91442-K 91442-M 91442-T
M1 *16* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA040Z-K RA040Z-M RA040Z-T
DCR: 150656-K 150656-M 150656-T
M1 *17* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA01PS-K RA01PS-M RA01PS-T RA0L0R-K RA0L0R-M RA0L0R-T
DCR: 107462-K 107462-M 107462-T 228101-K 228101-M 228101-T
M1 *18* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA01PZ-K RA01PZ-M RA01PZ-T
DCR: 91676-K 91676-M 91676-T
M1 *19* M417 M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905
DCN: RA0121-K RA0121-M RA0121-T
DCR: 184614-K 184614-M 184614-T
M1 *20* M423 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904

DCN: R24034-K R24034-M R24034-T
DCR: 91481-K 91481-M 91481-T

M2 *21* H4 H405 H484 H8 J4 J471 K0 L8 L814 L821 L831 M280 M315 M321 M332 M344 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00038-K R00038-M R00038-T
DCR: 159573-K 159573-M 159573-T 303-K 303-M 303-T

M2 *22* H4 H405 H484 H8 J5 J581 K0 L8 L818 L821 L831 M280 M311 M314 M321 M332 M342 M344 M349 M381 M392 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: RA64CM-K RA64CM-M RA64CM-T
DCR: 196509-K 196509-M 196509-T

M2 *23* F012 F013 F014 F015 F016 F123 H4 H405 H423 H484 H5 H521 H8 J4 J471 K0 L8 L814 L815 L822 L831 M280 M311 M315 M321 M332 M342 M344 M349 M373 M381 M391 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00241-K R00241-M R00241-T
DCR: 79488-K 79488-M 79488-T 79488-U

M2 *24* F012 F013 F014 F015 F016 F017 F019 F113 F123 H4 H405 H424 H483 H5 H521 H8 K0 L8 L814 L818 L822 L831 M1 M126 M141 M280 M311 M323 M342 M373 M393 M413 M431 M510 M522 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00135-K R00135-M R00135-T
DCR: 133509-U 2853-K 2853-M 2853-T 2853-U

M2 *25* F012 F013 F014 F015 F016 F123 H4 H405 H423 H484 H5 H521 H8 J4 J471 K0 L8 L814 L819 L822 L831 M280 M311 M315 M321 M332 M342 M344 M349 M373 M381 M391 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00292-K R00292-M R00292-T
DCR: 100051-K 100051-M 100051-T 100051-U

M2 *26* A119 A940 C017 C100 C730 C801 C803 C804 C805 C806 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01678-K R01678-M R01678-T
DCR: 127-K 127-M 127-T 127-U

M2 *27* A111 A940 C017 C100 C730 C801 C803 C804 C805 C806 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01706-K R01706-M R01706-T
DCR: 114-K 114-M 114-T 114-U

M2 *28* A430 A940 C017 C100 C730 C801 C803 C804 C805 C806 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R01703-K R01703-M R01703-T RA07Q2-K RA07Q2-M RA07Q2-T
DCR: 110843-K 110843-M 110843-T 72-K 72-M 72-T

M2 *29* C017 C100 C720 C730 C801 C803 C804 C805 C806 C807 M411 M417 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R06671-K R06671-M R06671-T
DCR: 130597-K 130597-M 130597-T

M2 *30* F012 F015 F423 J0 J011 J1 J111 J5 J521 L9 L941 M280 M320 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00671-K R00671-M R00671-T R10627-K R10627-M R10627-T
DCR: 151402-U 37837-K 37837-M 37837-T 37837-U

M2 *31* H4 H405 H484 H8 J4 J471 K0 L8 L814 L821 L831 M280 M315 M321 M332 M344 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00038-K R00038-M R00038-T
DCR: 159573-K 159573-M 159573-T 303-K 303-M 303-T 303-U

M2 *32* A119 A960 A970 C710 H4 H401 H481 H8 J0 J013 J1 J173 M280 M313 M321 M332 M344 M349 M381 M391 M411 M431 M510 M520 M530 M540 M620 M630 M640 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R16811-K R16811-M R16811-T

DCR: 104520-K 104520-M 104520-T 104520-U 129792-U 129991-U 130395-U 132222-U 133510-U 140723-U 140725-U 159060-U 191428-U 2471-U 250717-U 278358-U 278359-U 3589-U 849-U 87079-U 95073-U 95095-U 99996-U

M2 *33* A111 A960 C710 H4 H401 H481 H8 J0 J013 J1 J173 M280 M313 M321 M332 M344 M349 M381 M391 M411 M431 M510 M520 M530 M540 M620 M630 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R04004-K R04004-M R04004-T RA00DB-K RA00DB-M RA00DB-T
DCR: 104520-U 129792-U 129991-K 129991-M 129991-T 129991-U 130395-U 132222-U 133510-U 140723-U 140725-U 159060-U 191428-U 2471-U 250717-U 278358-U 278359-U 3589-K 3589-M 3589-T 3589-U 849-U 87079-U 95073-U 95095-U 99996-U

M2 *34* A119 A940 C101 C106 C108 C530 C730 C801 C802 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01202-K R01202-M R01202-T
DCR: 104516-K 104516-M 104516-T 104516-U

M2 *35* A119 A940 C106 C108 C530 C730 C801 C802 C803 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01391-K R01391-M R01391-T
DCR: 68-K 68-M 68-T 68-U

M2 *36* A119 A940 C101 C108 C550 C730 C801 C802 C804 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01512-K R01512-M R01512-T
DCR: 104530-K 104530-M 104530-T 104530-U

M2 *37* A111 A940 C101 C106 C108 C530 C730 C801 C802 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01151-K R01151-M R01151-T
DCR: 107317-K 107317-M 107317-T 107317-U

M2 *38* A111 A940 C106 C108 C530 C730 C801 C802 C803 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01287-K R01287-M R01287-T
DCR: 107324-K 107324-M 107324-T 107324-U 130928-U

M2 *39* A111 A940 C101 C108 C550 C730 C801 C802 C804 C805 C807 M411 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01514-K R01514-M R01514-T
DCR: 2-K 2-M 2-T 2-U

M2 *40* H1 H101 H182 H4 H401 H481 H8 J0 J011 J1 J171 M280 M315 M321 M332 M344 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R09442-K R09442-M R09442-T
DCR: 97308-K 97308-M 97308-T

M2 *41* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: **R00050-K R00050-M R00050-T R04769-K R04769-M R04769-T**
DCR: **108879-K 108879-M 108879-T 108879-U**

M2 *42* H1 H100 H181 J0 J012 J1 J171 J3 J371 M280 M313 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00115-K R00115-M R00115-T R04748-K R04748-M R04748-T
DCR: 129496-K 129496-M 129496-T 129496-U 133611-U 99344-U

M2 *43* D011 D601 H1 H100 H181 J0 J011 J1 J171 M280 M312 M321 M332 M343 M349 M371 M391 M412 M431 M511 M520 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00080-K R00080-M R00080-T
DCR: 6144-K 6144-M 6144-T 6144-U 6146-U

M2 *44* G013 G100 H1 H100 H181 H4 H401 H441 H8 J0 J011 J1 J171 M280 M312

M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M531 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01372-K R01372-M R01372-T
DCR: 129495-K 129495-M 129495-T 129495-U 132393-U 6139-U

M2 *45* H1 H100 H181 H4 H498 H9 J0 J011 J1 J171 M280 M312 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01628-K R01628-M R01628-T R12616-K R12616-M R12616-T
DCR: 132396-U 141452-U 188253-U 2466-U 8188-K 8188-M 8188-T 8188-U

M2 *46* H1 H100 H181 J0 J012 J1 J171 J3 J371 M280 M312 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00300-K R00300-M R00300-T R04745-K R04745-M R04745-T
DCR: 129499-K 129499-M 129499-T 129499-U 132388-U 8682-U

M2 *47* F012 F423 J0 J011 J1 J111 M280 M320 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01409-K R01409-M R01409-T R15414-K R15414-M R15414-T
DCR: 132391-U 2140-U 2634-K 2634-M 2634-T 2634-U

M2 *48* F012 F014 F423 H4 H401 H421 H8 J0 J011 J1 J111 M280 M320 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01383-K R01383-M R01383-T R15419-K R15419-M R15419-T
DCR: 42841-U 86970-K 86970-M 86970-T 86970-U

M2 *49* H1 H100 H181 J0 J012 J1 J172 M280 M313 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00116-K R00116-M R00116-T R04750-K R04750-M R04750-T
DCR: 129502-K 129502-M 129502-T 129502-U 132384-U 144395-U 1979-U

M2 *50* B415 B701 B713 B720 B815 B831 C108 C810 H1 H181 H4 H402 H482 H8 K0 L7 L722 M210 M211 M273 M283 M312 M313 M321 M332 M342 M343 M383 M392 M411 M431 M510 M520 M530 M540 M640 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: RA00JW-K RA00JW-M RA00JW-T
DCR: 99222-K 99222-M 99222-T 99222-U

M2 *51* J0 J013 J1 J171 J3 J372 M210 M211 M262 M281 M313 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R21793-K R21793-M R21793-T R21794-K R21794-M R21794-T
DCR: 191493-K 191493-M 191493-T

M2 *52* H4 H401 H481 H8 J0 J013 J1 J173 M280 M313 M321 M332 M344 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00419-K R00419-M R00419-T R07029-K R07029-M R07029-T
DCR: 104520-U 129792-U 129991-U 130395-U 132222-U 133510-U 140723-U 140725-U 159060-U 191428-U 2471-U 250717-U 278358-U 278359-U 3589-U 849-K 849-M 849-T 849-U 87079-U 95073-U 95095-U 99996-U

M2 *53* A111 A940 A960 A970 C710 C730 M411 M417 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R04810-K R04810-M R04810-T
DCR: 107360-K 107360-M 107360-T

M2 *54* A119 A940 A960 A970 C710 C730 M411 M417 M431 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R04811-K R04811-M R04811-T RA08AV-K RA08AV-M RA08AV-T
DCR: 104541-K 104541-M 104541-T 130216-K 130216-M 130216-T

M2 *55* H1 H100 H181 J0 J011 J1 J171 K0 L2 L250 M280 M314 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910

DCN: R01661-K R01661-M R01661-T R04740-K R04740-M R04740-T
DCR: 129510-K 129510-M 129510-T 129510-U 132386-U 138194-U 8685-U

M2 *56* H1 H100 H181 J0 J011 J1 J171 M280 M315 M321 M333 M340 M342 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01221-K R01221-M R01221-T R15416-K R15416-M R15416-T
DCR: 129498-K 129498-M 129498-T 129498-U 130280-U 2414-U 75192-U

M2 *57* H1 H100 H181 J0 J011 J1 J171 M280 M314 M321 M333 M340 M342 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00312-K R00312-M R00312-T R15415-K R15415-M R15415-T
DCR: 131311-U 6129-U 8181-K 8181-M 8181-T 8181-U 8193-U

M2 *58* H1 H101 H182 J0 J011 J1 J171 M280 M315 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01655-K R01655-M R01655-T R11509-K R11509-M R11509-T
DCR: 133908-U 147471-U 68180-U 8187-K 8187-M 8187-T 8187-U 8200-U

M2 *59* G010 G100 H1 H100 H181 J0 J011 J1 J171 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M531 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00243-K R00243-M R00243-T
DCR: 2407-U 8184-K 8184-M 8184-T 8184-U 8197-U

M2 *60* H1 H100 H181 J0 J011 J1 J171 M280 M315 M321 M333 M340 M342 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01258-K R01258-M R01258-T
DCR: 129497-K 129497-M 129497-T 129497-U 132385-U 98268-U

M2 *61* H1 H100 H181 H4 H401 H481 H8 J0 J011 J1 J171 M280 M313 M321 M331 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00480-K R00480-M R00480-T R15418-K R15418-M R15418-T
DCR: 129500-K 129500-M 129500-T 129500-U 132394-U 6268-U

M2 *62* F014 F521 H1 H100 H181 J0 J011 J1 J171 M280 M312 M321 M332 M343 M349 M371 M391 M413 M431 M510 M521 M530 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01636-K R01636-M R01636-T R04743-K R04743-M R04743-T
DCR: 129481-K 129481-M 129481-T 129481-U 132389-U 145033-U 72864-U

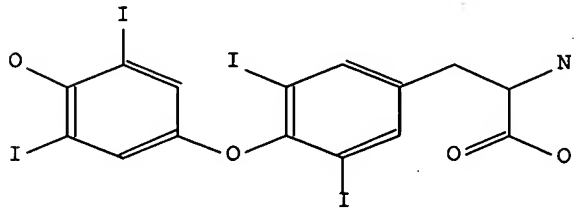
M2 *63* H1 H181 H4 H401 H481 H8 J0 J011 J1 J171 K0 L7 L722 M210 M211 M273 M283 M313 M321 M332 M343 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904
DCN: R12266-K R12266-M R12266-T
DCR: 90095-K 90095-M 90095-T

M2 *64* H1 H100 H181 K0 K4 K431 M280 M312 M321 M332 M342 M383 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00828-K R00828-M R00828-T
DCR: 73384-K 73384-M 73384-T 73384-U

M2 *65* H1 H100 H181 J0 J011 J1 J171 M280 M311 M321 M342 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00104-K R00104-M R00104-T R04091-K R04091-M R04091-T R13229-K R13229-M R13229-T
DCR: 133604-U 134730-U 2006-K 2006-M 2006-T 2006-U

M2 *66* H1 H100 H181 J0 J011 J1 J171 M280 M312 M321 M331 M340 M342 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01210-K R01210-M R01210-T R10414-K R10414-M R10414-T
DCR: 8189-K 8189-M 8189-T 8189-U 8214-U 8757-K 8757-M 8757-T

8757-U
M2 *67* H1 H100 H181 H4 H401 H481 H8 J0 J011 J1 J171 M280 M312 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R01654-K R01654-M R01654-T R15417-K R15417-M R15417-T
DCR: 6373-U 8182-K 8182-M 8182-T 8182-U
M2 *68* H1 H101 H182 J0 J012 J1 J172 K0 K2 K224 M280 M312 M322 M343 M349 M381 M392 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00117-K R00117-M R00117-T
DCR: 7460-U 92130-K 92130-M 92130-T 92130-U
M2 *69* H1 H100 H181 H5 H598 H9 J0 J011 J1 J171 M210 M211 M271 M281 M313 M321 M332 M343 M349 M381 M391 M416 M431 M620 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: R00187-K R00187-M R00187-T R03585-K R03585-M R03585-T
DCR: 132390-U 134498-U 21317-U 8186-K 8186-M 8186-T 8186-U
M6 *70* P420 P433 P714 P731 Q211 Q220 R280 M905
DRN 0038-U **0050-U** 0080-U 0104-U 0115-U 0116-U 0117-U 0135-U 0187-U 0241-U 0243-U 0292-U 0300-U 0312-U 0419-U 0480-U 0671-U 0828-U 1151-U 1202-U 1210-U 1221-U 1258-U 1287-U 1372-U 1383-U 1391-U 1409-U 1512-U 1514-U 1628-U 1636-U 1654-U 1655-U 1661-U 1678-U 1706-U 1833-U 1863-U
M2 *41* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P420 P433 P714 P731 Q211 Q220 M905 M904 M910
DCN: **R00050-K R00050-M R00050-T R04769-K R04769-M R04769-T**
DCR: **108879-K 108879-M 108879-T 108879-U**
AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 19 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-508920 [49] WPIX
TITLE: Pharmaceutical composition for thyroid hormones, includes glycerol, **gelatin** and liothyronine and/or **levothyroxine**
DERWENT CLASS: A11; A25; A32; A96; B05; P33
INVENTOR: DI M A; DI MARTINO A; GARAVANI A; MARCHIORRI M; MARTINO A D; MATEO A

PATENT ASSIGNEE: (ALTE-N) ALTELGON SA; (ALTE-N) ALTERGON SA; (GARA-I) GARAVANI A; (MARC-I) MARCHIORRI M; (MART-I) MARTINO A D; (MATE-I) MATEO A

COUNTRY COUNT: 34

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 1433478	A1	20040630	(200449)*	EN	57[0]	A61K009-00
CA 2454050	A1	20040627	(200449)	EN		A61K038-24
JP 2004210780	A	20040729	(200450)	JA	59	A61K031-198
US 20040219218	A1	20041104	(200473)	EN		A61K031-198

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1433478	A1	EP 2003-29729	20031223
CA 2454050	A1	CA 2003-2454050	20031223
US 20040219218	A1	US 2003-746386	20031223
JP 2004210780	A	JP 2003-432097	20031226

PRIORITY APPLN. INFO: IT 2002-MI2777 20021227

INT. PATENT CLASSIF.:

IPC RECLASSIF.: A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0047-10 [I,A] ; A61K0047-10 [I,C]; A61K0047-34 [I,A]; A61K0047-34 [I,C] ; A61K0047-42 [I,A]; A61K0047-42 [I,C]; A61K0009-00 [I,A] ; A61K0009-00 [I,C]; A61K0009-30 [I,C]; A61K0009-40 [I,A] ; A61K0009-48 [I,A]; A61K0009-48 [I,C]; A61P0005-00 [I,C] ; A61P0005-14 [I,A]

BASIC ABSTRACT:

EP 1433478 A1 UPAB: 20050706

NOVELTY - A pharmaceutical composition of thyroid hormones, comprises in the dried state, 31-60 weight% glycerol; 1-10 weight% water; and 30-68 weight% **gelatin** of bovine, pig or fish origin. It comprises liothyronine (T3) and/or **levothyroxine** or **levothyroxina** (T4) or their salts in 0.001-1 weight%, in a uniform matrix of soft-gel that can be taken by mouth without chewing, in which the matrix has the form and dimensions of a tablet or capsule.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a procedure for obtaining the above pharmaceutical composition comprising preparing a medicated gelatinous mixture comprising 10-50 weight% type A or B **gelatin** of bovine, pig or fish origin, 10-50 weight% glycerol, 0-10 weight% ethanol, 20-80 weight% water, and 0.001-1 weight% T3 and/or T4 or their salts; melting the medicated gelatinous mixture at 30-55degreesC (preferably 35-45degreesC) or at 30-80degreesC (preferably 40-65degreesC); feeding the mixture into the cavities of the shaping cylinders of a Rotary Die type machine for forming capsules; cutting and taking the pharmaceutical composition in a uniform matrix of soft-gel; drying the pharmaceutical composition in a uniform matrix of soft-gel. The medicated injected material comprises 30-95 (preferably 50-90) weight% glycerol, 0-50 (preferably 0-30) weight% ethanol, 0-50 (preferably 0-45) weight% water, 0-50 (preferably 5-20) weight% **gelatin**, and T3 and/or T4. After complete melting, the temperature of the gelatinous mixture is lowered to 45+/-5degreesC.

ACTIVITY - Antithyroid.

USE - Thyroid hormones intervene in the development, especially in the central nervous system and act in the adult, maintaining the metabolic homeostasis and influencing the function of all organs. Particularly T3 and T4 are useful for treating hypothyroidism. T4 is useful for suppressing the secretion of tyrotropin in the treatment of simple non-endemic goiter, chronic lymphocytic

thyroiditis and cancer of the thyroid. T4 sodium salt is used in combination with antithyroid agents in the treatment of thyrotoxicosis to prevent the onset of goiter and hypothyroidism.

ADVANTAGE - The composition provides a thyroid hormone formulation in a uniform matrix of soft gel which can be taken by mouth without chewing, and in which the matrix has the form and dimensions of a tablet or capsule. It allows safe and stable administration by mouth within the ambit of the narrow therapeutic index prescribed in the case of thyroid dysfunction.

MANUAL CODE: CPI: A03-C01; A12-V01; B04-C03C; B04-D01; B04-N02; B10-B02B; B10-E04C; B12-M11B; B12-M11C; B14-J01; B14-N11

TECH PHARMACEUTICALS - Preferred Composition: The composition comprises 32-55 (preferably 32.5-50) wt.% glycerol and 1-10 wt.% water. It comprises 0.5-5 wt.% ethanol. It may comprise 3-10 wt.% other polyhydroxy or polyether alcohols, preferably sorbitol/sorbitans, 1,2-propyleneglycol, polyethyleneglycols, and/or mannitol. It comprises excipients, e.g. solid additives that modify the characteristics of the release of thyroid hormones from the uniform matrix of soft-gel, or preservatives and/or coloring agents. It is provided on the outside with enteric layer(s) to facilitate ingestion.

TI Pharmaceutical composition for thyroid hormones, includes glycerol, **gelatin** and liothyronine and/or **levothyroxine**

TT TT: PHARMACEUTICAL COMPOSITION THYROID HORMONE GLYCEROL **GELATIN**

NOV NOVELTY - A pharmaceutical composition of thyroid hormones, comprises in the dried state, 31-60 wt.% glycerol; 1-10 wt.% water; and 30-68 wt.% **gelatin** of bovine, pig or fish origin. It comprises liothyronine (T3) and/or **levothyroxine** or **levothyroxina** (T4) or their salts in 0.001-1 wt.%, in a uniform matrix of soft-gel that can be taken by mouth without chewing, in which the matrix has the form and dimensions of a tablet or capsule.

DETD DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a procedure for obtaining the above pharmaceutical composition comprising preparing a medicated gelatinous mixture comprising 10-50 wt.% type A or B **gelatin** of bovine, pig or fish origin, 10-50 wt.% glycerol, 0-10 wt.% ethanol, 20-80 wt.% water, and 0.001-1 wt.% T3 and/or T4 or their salts; melting the medicated gelatinous mixture at 30-55degreesC (preferably 35-45degreesC) or at 30-80degreesC (preferably 40-65degreesC); feeding the mixture into the cavities of the shaping cylinders of a Rotary Die type machine for forming capsules; cutting and taking the pharmaceutical composition in a uniform matrix of soft-gel; drying the pharmaceutical composition in a uniform matrix of soft-gel. The medicated injected material comprises 30-95 (preferably 50-90) wt.% glycerol, 0-50 (preferably 0-30) wt.% ethanol, 0-50 (preferably 0-45) wt.% water, 0-50 (preferably 5-20) wt.% **gelatin**, and T3 and/or T4. After complete melting, the temperature of the gelatinous mixture is lowered to 45+/-5degreesC.

ABEX EXAMPLE - A medicated gelatinous mixture comprising (wt.%) **gelatin** (35.1), sorbitol/sorbitans (52.7), glycerin (8.1), **levothyroxine** (T4) (0.07), and water (4.03) was melted at 50degreesC. The mixture was kept at 45degreesC and fed into a rotary die type machine for forming capsules. The capsule-shaping cavities formed uniform matrices of soft-gel.

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 20 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-689534 [65] WPIX
DOC. NO. CPI: C2003-189021 [65]
DOC. NO. NON-CPI: N2003-550969 [65]
TITLE: Medical device for treating e.g. restenosis contains a coating, small molecule or antibody and/or its fragment

directed against an antigen on a progenitor endothelial cell surface

DERWENT CLASS: A96; B04; D16; D22; P31; P32; P34

INVENTOR: COTTONE R J; KULISZEWSKI M A; KUTRYK M; KUTRYK M J B; ROWLAND S M

PATENT ASSIGNEE: (COTT-I) COTTONE R J; (KULI-I) KULISZEWSKI M A; (KUTR-I) KUTRYK M J B; (ORBU-N) ORBUS MEDICAL TECHNOLOGIES INC; (ROWL-I) ROWLAND S M

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003065881	A2	20030814	(200365)*	EN	38[16]	
US 20030229393	A1	20031211	(200382)	EN		A61F002-06
AU 2003219718	A1	20030902	(200425)	EN		
EP 1471853	A2	20041103	(200472)	EN		
KR 2004105704	A	20041216	(200525)	KO		A61F002-06
JP 2005523050	W	20050804	(200552)	JA	54	A61L031-00
CN 1627924	A	20050615	(200563)	ZH		A61F002-06
AU 2003219718	A8	20051020	(200615)	EN		A61F002-06
US 20060135476	A1	20060622	(200642)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003065881	A2	WO 2003-US3645	20030206
US 20030229393	A1 CIP of	US 2001-808867	20010315
US 20030229393	A1 Provisional	US 2002-354680P	20020206
AU 2003219718	A1	AU 2003-219718	20030206
AU 2003219718	A8	AU 2003-219718	20030206
CN 1627924	A	CN 2003-803370	20030206
EP 1471853	A2	EP 2003-715988	20030206
JP 2005523050	W	JP 2003-565314	20030206
US 20030229393	A1	US 2003-360567	20030206
EP 1471853	A2	WO 2003-US3645	20030206
JP 2005523050	W	WO 2003-US3645	20030206
KR 2004105704	A	KR 2004-711431	20040723
US 20060135476	A1 Provisional	US 2000-189674P	20000315
US 20060135476	A1 Provisional	US 2000-201789P	20000504
US 20060135476	A1 CIP of	US 2001-808867	20010315
US 20060135476	A1 Provisional	US 2002-354680P	20020206
US 20060135476	A1 Div Ex	US 2003-360567	20030206
US 20060135476	A1	US 2005-297105	20051208

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
AU 2003219718	A1	Based on	WO 2003065881	A
EP 1471853	A2	Based on	WO 2003065881	A
JP 2005523050	W	Based on	WO 2003065881	A
AU 2003219718	A8	Based on	WO 2003065881	A
US 20060135476	A1	CIP of	US 7037332	B

PRIORITY APPLN. INFO: US 2002-354680P 20020206
US 2001-808867 20010315
US 2003-360567 20030206

US 2000-189674P 20000315
US 2000-201789P 20000504
US 2005-297105 20051208

INT. PATENT CLASSIF.:
MAIN: A61F002-06; A61L031-00
SECONDARY: A61F002-02; A61F002-04; A61L029-04
IPC ORIGINAL: A61F0002-06 [I,A]; A61F0002-06 [I,C]; A61F0002-82 [I,A]; A61F0002-82 [I,C]; A61K0031-716 [I,C]; A61K0031-721 [I,A]
IPC RECLASSIF.: A61B [I,S]; A61F0002-06 [I,A]; A61F0002-06 [I,C]; A61F0002-82 [I,C]; A61F0002-84 [I,A]; A61K0039-395 [I,A]; A61K0039-395 [I,C]; A61L [I,S]; A61L0017-00 [I,A]; A61L0017-00 [I,C]; A61L0027-00 [I,A]; A61L0027-00 [I,C]; A61L0029-00 [I,A]; A61L0029-00 [I,C]; A61L0031-00 [I,A]; A61L0031-00 [I,C]; A61M0001-14 [I,A]; A61M0001-14 [I,C]; A61M0025-00 [I,A]; A61M0025-00 [I,C]; A61M0029-02 [I,A]; A61M0029-02 [I,C]

BASIC ABSTRACT:

WO 2003065881 A2 UPAB: 20060120

NOVELTY - A medical device (D1) contains a coating, antibody and/or its fragment, and at least one compound (C1). The coating comprises at least one layer of a biocompatible matrix. The antibody or its fragment is directed against an antigen on a progenitor endothelial cell surface; and (C1) stimulates the progenitor endothelial cell to form an endothelium on the surface of (D1).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (1) a composition for coating (D1) comprising the biocompatible matrix, the antibody and/or antibody fragment and (C1); (2) coating (D1) involving application of at least one layer of the matrix to the surface of (D1), followed by application of the antibody or its fragment and at least one (C1) stimulating endothelial cell growth and differentiation, to the matrix; and (3) a device (D2) containing the coating and at least one small molecule. The small molecule interacts with the antigen and immobilizes the progenitor endothelial cell on the surface of (D2). ACTIVITY - Antiarteriosclerotic; Vasotropic; Thrombolytic; Cytostatic.

Fullerene-coated samples with and without antibodies were implanted into Yorkshire pigs. The stents were explanted for histology. Photomicrographs of cross sections through coronary artery explants of stents that had been implanted for 4 weeks showed that the fullerene coated explants inhibited excessive intimal hyperplasia at the stent site as compared to a bare stent control.

MECHANISM OF ACTION - None given.

USE - For treating vascular diseases e.g. atherosclerosis, restenosis, thrombosis, occlusion of a blood vessel and tubular organ; and for inhibiting intimal hyperplasia (claimed).

ADVANTAGE - The functional endothelium formed on the surface of the implanted device facilitates formation of confluent layer of the endothelial cell on the target blood vessel segment and hence inhibits neo-intimal hyperplasia. The medical device inhibits restenosis and thromboembolic complications resulting from device implantation over an extended period of time; reduces the morbidity and mortality of coronary artery atherosclerosis diseases; and improves the prognosis of the individuals being treated. The device has increased biocompatibility over the prior art, and decreases or inhibits migration and differentiation of smooth muscle cells, as well as collagen deposition along the inner luminal surface at the site of the implantation of the device.

TECH

INSTRUMENTATION AND TESTING - Preferred Device: (D1) and (D2) are selected from stent, stent graft, synthetic vascular graft, heart valve, catheter, vascular prosthetic filter, pacemaker, pacemaker lead, defibrilator, patent foramen ovale septal closure device, vascular clip, vascular

aneurysm occluder, hemodialysis graft, hemodialysis catheter, atrioventricular shunt, aortic aneurysm graft device, venous valve, suture, vascular anastomosis clip, indwelling venous catheter, indwelling arterial catheter, vascular sheath or drug delivery port (preferably stent). The stent additionally comprises a jacket, a covering or an encapsulation. The biocompatible matrix comprises C20-150 in the number of carbon atoms (preferably C60-70) fullerene, synthetic or naturally-occurring material. (D2) additionally comprises a compound (C1).
ORGANIC CHEMISTRY - Preferred Components: The naturally-occurring material of the matrix is collagen, elastin, laminin, fibronectin, vitronectin, heparin, fibrin, cellulose or amorphous carbon. The small molecule used in (D2) is peptide, glycopeptide, lipopeptide, lipid, saccharide, an organic molecule, an inorganic molecule or a nucleic acid. The small molecule is a ligand to the surface antigen.
BIOLOGY - Preferred Components: The surface antigen is CD133, CD34, CDw90, CD117, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2 or HAD-DR (preferably CD34, CD133 or Tie-2). (C1) is a growth factor selected from vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3 - FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta-1, acidic fibroblast growth factor, osteonectin, angiopoietin 1 or 2, insulin-like growth factor, granulocyte-macrophage colony-stimulating factor, platelet-derived growth factors AA, BB and AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, interleukin 8, **thyroxine**, or sphingosine 1-phosphate (preferably the VEGF family or Angiopoietin family, especially Ang-2). The progenitor endothelial cell is a human cell.
Preferred Antibody: The antibody is monoclonal, polyclonal, chimeric or humanized (preferably monoclonal antibody comprising large or small molecule of the antibody including Fab or F(ab')2 fragments), and specific for a human progenitor endothelial cell. The antibody or its fragment, or the small molecule is optionally covalently attached, or tethered covalently by a linker molecule to the outermost layer of the matrix coating (D1) or (D2) respectively. The antibody or its fragment is directed against the progenitor endothelial cell surface antigen. The antibody fragment comprises small molecules of synthetic or natural origin.
POLYMERS - Preferred Components: The encapsulation is cross-linked PVA hydrogel, ePTFE, PTFE, porous HDPE, polyurethane, or polyethylene terephthalate. The synthetic vascular graft comprises a material selected from cross-linked polyvinyl alcohol, ePTFE, PTFE, porous HDPE, polyurethane, and polyethylene terephthalate. The synthetic material of the matrix is polyurethane, segmented polyurethane-urea/heparin, poly-L-lactic acid, cellulose ester, polyethylene glycol, polyvinyl acetate, dextran or **gelatin** (preferably dextran, **gelatin** or fullerene). The fullerene is arranged as a nanotube.
INORGANIC CHEMISTRY - Preferred Components: The stent comprises material selected from stainless steel, NiTi, MP35N, and chromium alloy.
INSTRUMENTATION AND TESTING - Preferred Device: (D1) and (D2) are selected from stent, stent graft, synthetic vascular graft, heart valve, catheter, vascular prosthetic filter, pacemaker, pacemaker lead, defibrilator, patent foramen ovale septal closure device, vascular clip, vascular aneurysm occluder, hemodialysis graft, hemodialysis catheter, atrioventricular shunt, aortic aneurysm graft device, venous valve, suture, vascular anastomosis clip, indwelling venous catheter, indwelling arterial catheter, vascular sheath or drug delivery port (preferably stent). The stent additionally comprises a jacket, a covering or an encapsulation. The biocompatible matrix comprises C20-150 in the number of carbon atoms (preferably C60-70) fullerene, synthetic or

naturally-occurring material. (D2) additionally comprises a compound (C1).
ORGANIC CHEMISTRY - Preferred Components: The naturally-occurring material of the matrix is collagen, elastin, laminin, fibronectin, vitronectin, heparin, fibrin, cellulose or amorphous carbon. The small molecule used in (D2) is peptide, glycopeptide, lipopeptide, lipid, saccharide, an organic molecule, an inorganic molecule or a nucleic acid. The small molecule is a ligand to the surface antigen.
BIOLOGY - Preferred Components: The surface antigen is CD133, CD34, CDw90, CD117, HLA-DR, VEGFR-1, VEGFR-2, Muc-18 (CD146), CD130, stem cell antigen (Sca-1), stem cell factor 1 (SCF/c-Kit ligand), Tie-2 or HAD-DR (preferably CD34, CD133 or Tie-2). (C1) is a growth factor selected from vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)-3 - FGF-9, basic fibroblast growth factor, platelet-induced growth factor, transforming growth factor beta-1, acidic fibroblast growth factor, osteonectin, angiopoietin 1 or 2, insulin-like growth factor, granulocyte-macrophage colony-stimulating factor, platelet-derived growth factors AA, BB and AB, endothelial PAS protein 1, thrombospondin, proliferin, Ephrin-A1, E-selectin, leptin, heparin, interleukin 8, **thyroxine**, or sphingosine 1-phosphate (preferably the VEGF family or Angiopoietin family, especially Ang-2). The progenitor endothelial cell is a human cell.
Preferred Antibody: The antibody is monoclonal, polyclonal, chimeric or humanized (preferably monoclonal antibody comprising large or small molecule of the antibody including Fab or F(ab')2 fragments), and specific for a human progenitor endothelial cell. The antibody or its fragment, or the small molecule is optionally covalently attached, or tethered covalently by a linker molecule to the outermost layer of the matrix coating (D1) or (D2) respectively. The antibody or its fragment is directed against the progenitor endothelial cell surface antigen. The antibody fragment comprises small molecules of synthetic or natural origin.
POLYMERS - Preferred Components: The encapsulation is cross-linked PVA hydrogel, ePTFE, PTFE, porous HDPE, polyurethane, or polyethylene terephthalate. The synthetic vascular graft comprises a material selected from cross-linked polyvinyl alcohol, ePTFE, PTFE, porous HDPE, polyurethane, and polyethylene terephthalate. The synthetic material of the matrix is polyurethane, segmented polyurethane-urea/heparin, poly-L-lactic acid, cellulose ester, polyethylene glycol, polyvinyl acetate, dextran or **gelatin** (preferably dextran, **gelatin** or fullerene). The fullerene is arranged as a nanotube.
INORGANIC CHEMISTRY - Preferred Components: The stent comprises material selected from stainless steel, NiTi, MP35N, and chromium alloy.
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 21 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-065497 [07] WPIX
DOC. NO. CPI: C2004-027457 [07]
DOC. NO. NON-CPI: N2004-052949 [07]
TITLE: Stable immobilization of receptor and antibody in which proteins other than receptor to be immobilized coexist
DERWENT CLASS: B04; C07; D16; S03
INVENTOR: ISHIBASHI T; MATSUI K; NISHII S; OKA M
PATENT ASSIGNEE: (TOYM-C) TOYOBO KK
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
JP 2003302404	A	20031024	(200407)*	JA	10[5]	G01N033-543

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 2003302404 A		JP 2002-106890	20020409

PRIORITY APPLN. INFO: JP 2002-106890 20020409
INT. PATENT CLASSIF.:
IPC RECLASSIF.: C07K0017-00 [I,C]; C07K0017-08 [I,A]; G01N0033-53 [I,A]; G01N0033-53 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C] ; G01N0033-566 [I,A]; G01N0033-566 [I,C]

BASIC ABSTRACT:

JP 2003302404 A UPAB: 20050528

NOVELTY - Stable immobilization (M1) of receptor and antibody in which proteins other than receptor to be immobilized coexist, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a composition (I) of the immobilized receptor produced by (M1); (2) measuring (M2) a substance using (I) by competing method; and (3) a kit for (M2), comprising (I).

USE - (M1) is useful for stable immobilization of a receptor. (I) is useful for measuring a substance by competing method (claimed).

ADVANTAGE - The method is effective and efficient. DESCRIPTION OF DRAWINGS - The figure shows the activity antibody solid phase (drawing includes non-English language text). MANUAL CODE: CPI: B04-B04C; B04-G01; B04-K01; B04-N01; B04-N02; B04-N03; B04-N04; B11-C07A; B12-K04E; B14-L01; B14-L06; C04-B04C; C04-G01; C04-K01; C04-N01; C04-N02; C04-N03; C04-N04; C11-C07A; C12-K04E; C14-L01; C14-L06; D05-H07; D05-H09; D05-H11
EPI: S03-E14H4

TECH

BIOTECHNOLOGY - Preferred Method: In (M1), the protein other than the receptor for immobilization do not interfere in joint reaction which the receptor recognizes and does not interact with the receptor. Proteins other than the receptor to immobilize is antibody, albumin, milk protein, **gelatin**, chaperonin or saccharide binding protein. The saccharide binding proteins couples with the carbohydrate which the receptor has. The antibody is immunoglobulin G, M, D or A of fish, amphoterics, reptiles or mammal, preferably rodent teeth origin of mammal. Antibody is the fragment of constant region of an immunoglobulin. The albumin, milk protein, **gelatin** is of birds, fish, amphoterics, reptile or mammalian origin. The saccharide binding protein is derived from micro organism, plants, birds, fish, amphoterics or mammals, preferably are microorganisms derived maltose binding protein (MBP), sucrose binding protein or a plant lectin. The plant lectins are concanavalin A and wheat germ lectin. The receptor is an antibody, receptor in a nucleus, a transmembrane type receptor, a transporter, a co-factor or a coactivator. The receptor recognizes a low molecular weight compound which has hormone action or biological action. The low molecular weight compounds are an estradiol, testosterone, an androsterone, a progesterone, dihydro testosterone, mibolerone, R1881, diethyl stilbestrol, **thyroxine**, the tri iodo thyronine, the estriol, bisphenol A, an alkylphenol, agrochemicals, antiseptic an antifungal agent, antibiotics, PCBs, and dioxins. The receptor is androgen receptor (AR) an estrogen receptor (ER), a glucocorticoid receptor (GR), a mineralocorticoid receptor (MCR), a progesterone receptor (PR), a vitamin-D receptor (VDR), the Thyroid receptor (TR), a retinoic-acid receptor (RAR), a retinoid receptor (AHR), an allyl hydrocarbon receptor (AHR), pregnane receptor, peroxisome proliferator-activated receptors (PPAR) or its variants.

BIOTECHNOLOGY - Preferred Method: In (M1), the protein other than the receptor for immobilization do not interfere in joint reaction which the receptor recognizes and does not interact with the receptor. Proteins other than the receptor to immobilize is antibody, albumin, milk protein, **gelatin**, chaperonin or saccharide binding protein. The saccharide binding proteins couples with the carbohydrate which the receptor has. The antibody is immunoglobulin G, M, D or A of fish, amphoterics, reptiles or mammal, preferably rodent teeth origin of mammal. Antibody is the fragment of constant region of an immunoglobulin. The albumin, milk protein, **gelatin** is of birds, fish, amphoterics, reptile or mammalian origin. The saccharide binding protein is derived from micro organism, plants, birds, fish, amphoterics or mammals, preferably are microorganisms derived maltose binding protein (MBP), sucrose binding protein or a plant lectin. The plant lectins are concanavalin A and wheat germ lectin. The receptor is an antibody, receptor in a nucleus, a transmembrane type receptor, a transporter, a co-factor or a coactivator. The receptor recognizes a low molecular weight compound which has hormone action or biological action. The low molecular weight compounds are an estradiol, testosterone, an androsterone, a progesterone, dihydro testosterone, mibolerone, R1881, diethyl stilbestrol, **thyroxine**, the tri iodo thyronine, the estriol, bisphenol A, an alkylphenol, agrochemicals, antiseptic an antifungal agent, antibiotics, PCBs, and dioxins. The receptor is androgen receptor (AR) an estrogen receptor (ER), a glucocorticoid receptor (GR), a mineralocorticoid receptor (MCR), a progesterone receptor (PR), a vitamin-D receptor (VDR), the Thyroid receptor (TR), a retinoic-acid receptor (RAR), a retinoid receptor (AHR), an allyl hydrocarbon receptor (AHR), pregnane receptor, peroxisome proliferator-activated receptors (PPAR) or its variants.
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 22 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-314136 [31] WPIX
DOC. NO. CPI: C2003-082409 [31]
TITLE: Composition used for treating hypothyroidism comprises thyroid hormones in capsules or swallowable uniform soft gel matrices
DERWENT CLASS: A96; B05
INVENTOR: DI M A; DI MARTINO A; GARAVANI A; MARCHIORRI M; MATEO E A; MATEO ECHANAGORRIA A
PATENT ASSIGNEE: (ALTE-N) ALTELGON SA; (ALTE-N) ALTERGON SA; (DMAR-I) DI MARTINO A; (GARA-I) GARAVANI A; (MARC-I) MARCHIORRI M; (ECHA-I) MATEO ECHANAGORRIA A
COUNTRY COUNT: 33

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
CA 2392545	A1	20030102	(200331)*	EN	24[0]	
EP 1291021	A2	20030312	(200331)	EN		
JP 2003081870	A	20030319	(200331)	JA	35	A61K038-23
US 20030050344	A1	20030313	(200331)	EN		
IT 1325723	B	20041221	(200560)	IT		A61K031-00
EP 1291021	B1	20051214	(200602)	EN		
DE 60207951	E	20060119	(200614)	DE		
ES 2254559	T3	20060616	(200641)	ES		
DE 60207951	T2	20060803	(200651)	DE		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CA 2392545 A1		CA 2002-2392545	20020628
IT 1325723 B		IT 2001-MI1401	20010702
DE 60207951 E		DE 2002-607951	20020702
EP 1291021 A2		EP 2002-14594	20020702
EP 1291021 B1		EP 2002-14594	20020702
DE 60207951 E		EP 2002-14594	20020702
ES 2254559 T3		EP 2002-14594	20020702
JP 2003081870 A		JP 2002-193024	20020702
US 20030050344 A1		US 2002-188467	20020702
DE 60207951 T2		DE 2002-607951	20020702
DE 60207951 T2		EP 2002-14594	20020702

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
DE 60207951	E	Based on	EP 1291021	A
ES 2254559	T3	Based on	EP 1291021	A
DE 60207951	T2	Based on	EP 1291021	A

PRIORITY APPLN. INFO: IT 2001-MI1401 20010702
INT. PATENT CLASSIF.:

MAIN:	A61K031-00
SECONDARY:	A61K
IPC ORIGINAL:	A61K0038-24 [I,A]; A61K0038-24 [I,A]; A61K0038-24 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,A]; A61K0009-48 [I,C]
IPC RECLASSIF.:	A61K0038-22 [I,A]; A61K0038-22 [I,C]; A61K0038-23 [I,A]; A61K0038-23 [I,C]; A61K0047-02 [I,C]; A61K0047-04 [I,A]; A61K0047-10 [I,A]; A61K0047-10 [I,C]; A61K0047-12 [I,A]; A61K0047-12 [I,C]; A61K0047-24 [I,A]; A61K0047-24 [I,C]; A61K0047-26 [I,A]; A61K0047-26 [I,C]; A61K0047-34 [I,A]; A61K0047-34 [I,C]; A61K0047-36 [I,A]; A61K0047-36 [I,C]; A61K0047-38 [I,A]; A61K0047-38 [I,C]; A61K0047-42 [I,A]; A61K0047-42 [I,C]; A61K0009-06 [I,A]; A61K0009-06 [I,C]; A61K0009-10 [I,A]; A61K0009-10 [I,C]; A61K0009-14 [I,A]; A61K0009-14 [I,C]; A61K0009-16 [I,A]; A61K0009-16 [I,C]; A61K0009-28 [I,A]; A61K0009-28 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,C]; A61P0001-00 [I,A]; A61P0001-00 [I,C]; A61P0025-00 [I,C]; A61P0025-22 [I,A]; A61P0003-00 [I,A]; A61P0003-00 [I,C]; A61P0003-04 [I,A]; A61P0005-00 [I,C]; A61P0005-14 [I,A]

BASIC ABSTRACT:

CA 2392545 A1 UPAB: 20060202

NOVELTY - Composition comprises thyroid hormones in capsules or swallowable uniform soft gel matrices, preferably comprising **gelatin.**

ACTIVITY - Antithyroid.

No biological tests or results are given in the source material.

MECHANISM OF ACTION - None given in the source material.

USE - Used for treating hypothyroidism.

ADVANTAGE - The composition can be prepared to minimize degradation of the hormones and provides high and rapid bioavailability. MANUAL CODE: CPI: A12-V01; B04-C02A; B04-C03C; B10-B02E; B10-E04C; B14-N11

TECH

PHARMACEUTICALS - Preferred Composition: The thyroid hormones are **thyroxine** (T4) and/or triiodothyronine (T3), optionally in sodium salt form. The capsules are hard or soft capsules. The hormones are in the form of a powder, micropellets or non-compacted microgranules containing

conventional excipients e.g. dicalcium phosphate dihydrate, or are dispersed in a liquid or semi liquid vehicle, especially ethanol and/or glycerol. The composition has an enteric coating or an ingestion facilitating coating. The capsule or matrix material includes a plasticizer, especially glycerol, propylene glycol or a sorbitol/sorbitan solution.

POLYMERS - Preferred Components: The capsules or matrices comprise type A or B **gelatin**, methylcellulose, hydroxypropyl cellulose or calcium alginate. The composition includes a liquid or semi liquid vehicle e.g. a polysorbate or polyoxyethylene sorbitan fatty acid ester.

NOV NOVELTY - Composition comprises thyroid hormones in capsules or swallowable uniform soft gel matrices, preferably comprising **gelatin.**

PHARMACEUTICALS - Preferred Composition: The thyroid hormones are **thyroxine** (T4) and/or triiodothyronine (T3), optionally in sodium salt form. The capsules are hard or soft capsules. The hormones are in the form of a powder, micropellets or non-compacted microgranules containing conventional excipients e.g. dicalcium phosphate dihydrate, or are dispersed in a liquid or semi liquid vehicle, especially ethanol and/or glycerol. The composition has an enteric coating or an ingestion facilitating coating. The capsule or matrix material includes a plasticizer, especially glycerol, propylene glycol or a sorbitol/sorbitan solution.

POLYMERS - Preferred Components: The capsules or matrices comprise type A or B **gelatin**, methylcellulose, hydroxypropyl cellulose or calcium alginate. The composition includes a liquid or semi liquid vehicle e.g. a polysorbate or polyoxyethylene sorbitan fatty acid ester.

ABEX EXAMPLE - Dry-filled hard **gelatin** capsules contained granules comprising **thyroxine**, dicalcium phosphate dihydrate, sodium carboxymethyl starch, microcrystalline cellulose and magnesium stearate (no quantities given).

IT UPIT 20060202
; **108879-CL**; 99443-CL; 490-CL; 861-CL; 107456-CL; 95972-CL; 100739-CL; 97485-CL; 89822-CL; 104476-CL

CMC UPB 20060202
DRN: 0032-U **0050-U** 0113-U 0137-U 1653-U 1860-U 1866-U
DCR: 100739-U 107307-U 107456-U **108879-U** 133925-U 134009-U 490-U 861-U 89822-U 99443-U
M1 *06* M423 M431 M782 M905 M904
DCN: R24033-K R24033-M
DCR: 95972-K 95972-M
M1 *07* H5 H521 H8 M210 M211 M272 M281 M320 M423 M431 M782 M905 M904 M910
DCN: R01860-K R01860-M RA02KX-K RA02KX-M
DCR: 100739-K 100739-M 100739-U 199366-K 199366-M
M1 *08* H4 H401 H481 H5 H521 H8 M280 M313 M321 M332 M342 M383 M391 M423 M431 M782 M905 M904
DCN: R03005-K R03005-M
DCR: 135340-K 135340-M 97485-K 97485-M
M1 *09* A220 A960 C710 J0 J011 J1 J111 M423 M431 M630 M782 M905 M904 M910
DCN: R11203-K R11203-M
DCR: 107307-U 133925-U 134009-U 89822-K 89822-M 89822-U
M1 *10* F012 F013 F014 F113 H4 H401 H481 H5 H522 H589 H8 M210 M212 M272 M283 M312 M322 M332 M342 M343 M373 M383 M391 M423 M431 M510 M521 M530 M540 M782 M905 M904
DCN: RA014C-K RA014C-M
DCR: 104476-K 104476-M
M2 *01* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343

M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P624 M905
M904 M910
DCN: **R00050-K R00050-M R00050-T**
R04769-K R04769-M R04769-T
DCR: **108879-K 108879-M 108879-T**
108879-U

M2 *02* G015 G017 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609
H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343
M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P624 M905
M904 M910
DCN: R01653-K R01653-M R01653-T R06386-K R06386-M R06386-T
DCR: 99443-K 99443-M 99443-T 99443-U

M2 *03* H4 H403 H483 H8 M280 M313 M321 M332 M343 M383 M391 M416 M431
M620 M782 M905 M904 M910
DCN: R00113-K R00113-M
DCR: 490-K 490-M 490-U

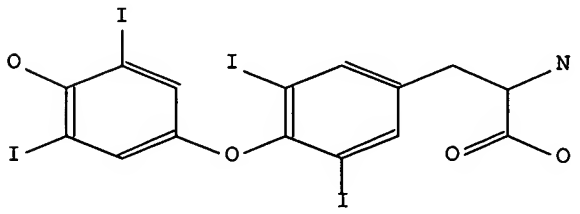
M2 *04* H4 H402 H482 H8 M280 M313 M321 M331 M342 M383 M391 M416 M431
M620 M782 M905 M904 M910
DCN: R00137-K R00137-M
DCR: 861-K 861-M 861-U

M2 *05* H4 H405 H484 H8 K0 L8 L814 L821 L833 M280 M315 M321 M332 M344
M383 M391 M416 M431 M620 M782 M905 M904 M910
DCN: R00032-K R00032-M
DCR: 107456-K 107456-M 107456-U

DRN 0032-U **0050-U** 0113-U 0137-U 1653-U 1860-U 1866-U

M2 *01* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609
H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343
M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P624 M905
M904 M910
DCN: **R00050-K R00050-M R00050-T**
R04769-K R04769-M R04769-T
DCR: **108879-K 108879-M 108879-T**
108879-U

AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 23 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-239076 [23] WPIX
DOC. NO. CPI: C2003-061183 [23]
TITLE: Composition useful for the treatment of respiratory, lung

and malignant diseases comprises a non-glucocorticoid steroid or its salt and/or ubiquinone or its salt

DERWENT CLASS: A96; B05; B07; C03

INVENTOR: NYCE J W

PATENT ASSIGNEE: (EPIG-N) EPIGENESIS PHARM INC; (NYCE-I) NYCE J W; (UYEC-N) UNIV EAST CAROLINA

COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002085297	A2	20021031	(200323)*	EN	51[4]	A61K000-00
US 20040082522	A1	20040429	(200429)	EN		A61K031-704
AU 2002303427	A1	20021105	(200433)	EN		
AU 2002303427	A8	20051013	(200611)	EN		A61K031-56

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002085297	A2	WO 2002-US12555	20020422
US 20040082522	A1 Provisional	US 2001-286124P	20010424
AU 2002303427	A1	AU 2002-303427	20020422
US 20040082522	A1 CIP of	WO 2002-US12555	20020422
US 20040082522	A1	US 2003-454061	20030603
AU 2002303427	A8	AU 2002-303427	20020422

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002303427	A1 Based on	WO 2002085297 A
AU 2002303427	A8 Based on	WO 2002085297 A

PRIORITY APPLN. INFO: US 2001-286124P 20010424
WO 2002-US12555 20020422
US 2003-454061 20030603

INT. PATENT CLASSIF.:
MAIN: A61K-00; A61K031-56
SECONDARY: A61K031-12
IPC RECLASSIF.: A61K0031-122 [I,A]; A61K0031-122 [I,C]; A61K0031-56 [I,A] ; A61K0031-56 [I,C]; A61K0031-568 [I,C]; A61K0031-5685 [I,A]; A61K0031-66 [I,A]; A61K0031-66 [I,C]; A61K0031-7028 [I,C]; A61K0031-704 [I,A]; C12N0005-02 [I,A]; C12N0005-02 [I,C]; C12N0005-22 [I,A]; C12N0005-22 [I,C]

BASIC ABSTRACT:

WO 2002085297 A2 UPAB: 20050528

NOVELTY - A pharmaceutical or veterinary composition comprises a combination of non-glucocorticoid steroid or its salt and/or ubiquinone or its salt and a carrier or diluent.

DETAILED DESCRIPTION - A pharmaceutical or veterinary composition (C1) comprises an active agent (A1) selected from a non-glucocorticoid steroid of formula (I), (III) or (IV) or its ester, thioester, ether, thioether, inorganic ester, monosaccharide, disaccharide, or oligosaccharide and salt and/or ubiquinone ((CoQ)n') of formula (II) or its salt and a carrier or diluent. a = single or double bond;

R = H or halo;

R1 = H or SO2OM;

M = H, Na, -SO2O-CH2CH(OCOR2)CH2OCOR3 or -P(O)2-O- CH2CH(OCOR2)CH2OCOR3;
R2 and R3 = optionally branched 1-14C alkyl or glucuronide; R1 - R4, R7 - R10, R12 - R14 and R19 = T1 or OR; R5 = R4 and R11;
R11 = T2, SH or Q1;
Q1 = spirooxirane, spirothirane, -OSO2R20 or -OPOR20R21; R15 = T1 - T4;
T1 = H, halo, 1-10C alkyl or 1-10C alkoxy; T2 = H, halo, OH or 1-10C alkyl; T3 = H, halo, 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, formyl, 1-10C alkanoyl or epoxy;
T4 = OR, SH, H, halo or Q1; R16 = -C(O)OR22 or T2;
R17 and R18 = OH, T1, Q2;
Q2 = H, 1-10C alkylamino, ((1-10C)alkyl)n-amino-(1-10C)alkyl, 1-10C alkoxy, OH-(1-10C)alkyl, 1-10C alkoxy-(1-10C)alkyl, (halo)m(1-10C)alkyl, 1-10C alkanoyl, formyl, 1-10C carbalkoxy or 1-10C alkanoyloxy;
R6 = H, OR, halo, 1-10C alkyl or C(O)OR22; R5+R6, R10+R11, R15+R16, and R17+R18 = =O; C(R17+R18) = 3 - 6 membered ring optionally containing O atom;
C(R15+R17) = epoxide;
R20 and R21 = OH;
R22 = H, (halo)m(1-10C)alkyl or 1-10C alkyl; n = 0 - 2;
m = 1 3;
n' = 1 - 12.
Provided that:
(1) When R16 is -C(O)OR22, R15 is T1; (2) When R16 is halo, OH or 1-10C alkyl, R15 is T2; (3) When R16 is OH, R15 is T3; (4) When R16 is H, R15 is T4; (5) When R6 is H, OR, halo, 1-10C alkyl or C(O)OR22, R17 and R18 is T1 or OH; (6) When R15+R16 is =O, R17 and R18 is Q2; and (7) The H at position 5 of formula (I) is present in alpha or beta configuration or formula (I) comprises a racemic mixture of both configurations.
INDEPENDENT CLAIMS are also included for the following: (1) A delivery kit containing in separate containers, (A1) and a delivery device; and
(2) An in vivo method of preventing or treating a disorder or condition associated with abnormal levels of adenosine or adenosine receptors involving simultaneous, sequential or separate administration of (A1) (preferably DHEA-S (dehydroepiandrosterone- sulfate) or DHEA (dehydroepiandrosterone)), where when DHEA is the sole agent and the diseases or condition is steroid induced asthma, (C1) may not comprise a corticosteroid.
ACTIVITY - Antiasthmatic; Antiinflammatory; Cytostatic; Antiallergic; Analgesic.
MECHANISM OF ACTION - Glucose-6-phosphate dehydrogenase inhibitor.
USE - For the prophylactic, therapeutic or preventive treatment of a respiratory, lung or malignant disorder or condition e.g. bronchoconstriction, lung inflammation or allergies, wheezing, difficulty breathing, impeded airways or lung pain, asthma, chronic obstructive pulmonary disease, cystic fibrosis, acute respiratory distress syndrome, infantile respiratory distress syndrome, pulmonary fibrosis, bronchitis, allergic rhinitis, decreased lung surfactants and cancer (e.g. lung cancer) (all claimed).
ADVANTAGE - (C1) reduces or depletes the adenosine levels and increases lung surfactant levels or ubiquinone in a subject. (C1) is effective, less costly and devoid of significant detrimental side effects.

MANUAL CODE: CPI: A12-V01; B01-D01; B01-D02; B10-A06; B14-C01; B14-C03; B14-D03; B14-F02B; B14-G02A; B14-H01; B14-K01; B14-L06; B14-S12; C01-D01; C01-D02; C10-A06; C14-C01; C14-C03; C14-D03; C14-F02B; C14-G02A; C14-H01; C14-K01; C14-L06; C14-S12

TECH

PHARMACEUTICALS - Preferred Composition: (C1) comprises 0.05 - 40 (preferably 1 - 20) w/w.% of (A1). When the carrier or diluent is a solid or liquid carrier, (A1) comprises solid or liquid particles. The carrier is a hydrophobic carrier. (C1) further comprises an agent (A2) selected from other therapeutic agents, preservatives, anti-oxidants, flavoring agents, volatile oils, buffering agents, dispersants or surfactants. A

lozenge further comprises a flavoring agent selected from sucrose, acacia or tragacanth, or pastilles. The pastilles additionally comprise an inert base selected from **gelatin**, glycerin, sucrose or acacia. The solution, suspension or emulsion of the oral formulation is selected from non-aqueous liquid solution or suspension, or oil in water or water in oil emulsion. A oral formulation further comprises an enteric coating. A injectable solutions or suspensions further comprise other therapeutic agents, antioxidants, buffers, bacteriostatic agents or solutes, which render the solution or suspension isotonic with the blood of any intended recipient. A sterile aqueous or non-aqueous injection solutions or suspensions further comprise suspending agents or thickening agents. A topical formulation further comprises a carrier selected from vaseline, lanoline polyethylene glycol, alcohol or transdermal enhancers. An iontophoretic formulation further comprises a buffer. An inhalable or respirable formulation further comprises (A2) or powdered or liquid particles of (A1) having a size of 0.05 - 10 (preferably 0.1 - 5) mum. A nasal, intrapulmonary or intratracheal formulation comprises powdered or liquid particles of (A1) having a size of 8 - 100 (preferably 10 - 50) mum. (C1) is freeze-dried or lyophilized.
Preferred Method: The in vivo method further involves administering another therapeutic or diagnostic agent.
Preferred Components: The other therapeutic or diagnostic agent selected from component P1, P2 or P3. P1 is analgesic, pre-menstrual medication, menopausal agent, anti-aging agent, anti-anxyolytic agent, mood disorder agent, anti-depressant, anti-bipolar mood agent, anti-schyzophrenic agent, anti-cancer agent, alkaloid, blood pressure controlling agent, hormone, anti-inflammatory agent, muscle relaxant, steroid, soporific agent, anti-ischemic agent, anti-arrythmic agent, contraceptive, vitamin, mineral, tranquilizer, neurotransmitter regulating agent, wound and burn healing agent, anti-angiogenic agent, cytokine, growth factor, anti-metastatic agent, antacid, anti-histaminic agent, anti-bacterial agent, anti-viral agent, anti-gas agent, appetite suppressant, sun screen, emolient, skin temperature lowering product, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agent, libido altering agent, bile acid, laxative, anti-diarrheic agent, skin renewal agent, hair growth agent, anti-menopausal agent such as hormone, nociceptic agent, other agents useful for the treatment of diseases associated or accompanied with pain and inflammation such as arthritis, burns, wounds, chronic bronchitis, chronic obstructive pulmonary disease, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, autoimmune disease such as lupus erythematosus, agent for reperfusion injury or counteracting appetite suppressant. P2 is a hormone selected from female and male sex hormone, **thyroxine** or glucocorticoid, sedative, selected from diphenhydramine, hydroxyzine, methotrimeprazine, promethazine, protofol, melatonin, trimeprazzine, amitriptyline HCl, chlordiazepoxide, amobarbital, secobarbital, aprobarbital, butabarbital, ethchiorvynol, glutethimide, L-tryptophan, mephobarbital, methohexital Na, midazolam HCl, oxazepam, pentobarbital Na, Phenobarbital, secobarbital Na or thiamylal Na; libido altering agent selected from Viagra or other NO-level modulating agent; analgesic selected from acetominophen, anilerdine, aspirin, buprenorphine, butabital, butorpphanol, choline salicylate, codeine, dezocine, diclofenac, diflunisal, dihydrocodeine, elcatoninin, etodolac, fenoprofen, hydrocodone, hydromorphone, ibuprofen, ketoprofen, ketorolac, levorphanol, magnesium salicylate, meclofenamate, mefenamic acid, meperidine, methadone, methotrimeprazine, morphine, nalbuphine, naproxen, opium, oxycodon, oxymorphone, pentazocine, Phenobarbital, propoxyphene, salicylic acid, tramadol, narcotic analgesic, ibuprofen, acetyl salicylate, oruda, aleve, acetaminofen or controlled substance selected from morphine or codeine; anti-depressant selected from tricyclics, MAO inhibitor or epinephrine, gamma-amino butyric acid,

chlordiazepoxide, amitriptyline, loxapine maprotiline and perphenazine, dopamine or serotonin level elevating agent selected from prozac, amytryptilin, wellbutrin or Zoloft; skin renewal agent; hair growth agent; anti-anxiety agent selected from alprazolam, bromazepam, buspirone, chlordiazepoxide, chlormezanone, clorazepate, diazepam, halazepam, hydroxyzine, ketaszolam, lorazepam, meprobamate, oxazepam or prazepam; anti-inflammatory agent selected from non-steroidal anti-inflammatory drug, diclofenac, beclomethaxone, budesonide, dexamethasone, flunisolide, triamcinolone, flurbiprofen, indomethacin, ketorolac, rimexolone, non-rheumatic aspirin, choline salicylate, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, magnesium salicylate, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozen, phenylbutazone, piroxicam, salsalate, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid, tolmetin or glucocorticosteroid; soporific selected from melatonin, diazepam, cytoprotective, anti-ischemic , agent for the treatment of head injuries or alprazolam, bromozepam, diazepam, diphenylhydramine, doxylamine, estazolam, flurazepam, halazepam, ketazolam, lorazepam, nitrazepam, prazepam quazepam, temazepam, triazolam, zolpidem or sopiclone. P3 is a therapeutic or diagnostic agent for the treatment of brain injury/ischemia; cytoprotective agent and agent for the treatment of menopause or menopausal symptoms selected from ergotamine, belladonna alkaloid, Phenobarbital, clonidine, conjugated estrogen, medroxyprogesterone, estradiol, estradiol cypionate, estradiol valerate, estrogen, conjugated estrogen, esterified estrone, estropipate or ethinyl estradiol; agent for the treatment of symptoms of premenstrual syndrome selected from progesterone, progestin, gonadotrophic releasing hormone, oral contraceptive, danazol, luprolide acetate or vitamin B6; agent for the treatment of emotional/psychiatric symptoms selected from tricyclic anti-depressants selected from amitriptyline HCl (elavil), amitriptyline HCl, perphenazine (triavil) or doxepine HCl (sinequan), diazepam (valium), lorazepam (ativan), alprazolam (xanax), selective serotonin reuptake inhibitor, fluoxetine HCl (prozac), sertaline HCl (zoloft), paroxetine HCl (paxil), fluvoxamine maleate (luvox), venlafaxine HCl (effexor), serotonin, serotonin agonist (fenfluramine); or anti-migraine agent.
Preferred Kit: (A1) is provided as inhalable, respirable, intrapulmonary or nasal formulation. The delivery device comprises an inhaler provided with an aerosol or aerosol or spray generator that delivers particles having a size of 0.05 - 10 micron in size or about 8 - 100 micron in size. The delivery device delivers individual pre-metered doses of (C1) and comprises an inhaler (preferably compression inhaler) and a nebulizer or insufflator. (A1) is provided as a formulation in a pierceable or openable capsule or cartridge.
PHARMACEUTICALS - Preferred Composition: (C1) comprises 0.05 - 40 (preferably 1 - 20) w/w.% of (A1). When the carrier or diluent is a solid or liquid carrier, (A1) comprises solid or liquid particles. The carrier is a hydrophobic carrier. (C1) further comprises an agent (A2) selected from other therapeutic agents, preservatives, anti-oxidants, flavoring agents, volatile oils, buffering agents, dispersants or surfactants. A lozenge further comprises a flavoring agent selected from sucrose, acacia or tragacanth, or pastilles. The pastilles additionally comprise an inert base selected from **gelatin**, glycerin, sucrose or acacia. The solution, suspension or emulsion of the oral formulation is selected from non-aqueous liquid solution or suspension, or oil in water or water in oil emulsion. A oral formulation further comprises an enteric coating. A injectable solutions or suspensions further comprise other therapeutic agents, antioxidants, buffers, bacteriostatic agents or solutes, which render the solution or suspension isotonic with the blood of any intended recipient. A sterile aqueous or non-aqueous injection solutions or suspensions further comprise suspending agents or thickening agents. A

topical formulation further comprises a carrier selected from vaseline, lanoline polyethylene glycol, alcohol or transdermal enhancers. An iontophoretic formulation further comprises a buffer. An inhalable or respirable formulation further comprises (A2) or powdered or liquid particles of (A1) having a size of 0.05 - 10 (preferably 0.1 - 5) mum. A nasal, intrapulmonary or intratracheal formulation comprises powdered or liquid particles of (A1) having a size of 8 - 100 (preferably 10 - 50) mum. (C1) is freeze-dried or lyophilized.
Preferred Method: The in vivo method further involves administering another therapeutic or diagnostic agent.
Preferred Components: The other therapeutic or diagnostic agent selected from component P1, P2 or P3. P1 is analgesic, pre-menstrual medication, menopausal agent, anti-aging agent, anti-anxyolytic agent, mood disorder agent, anti-depressant, anti-bipolar mood agent, anti-schyzophrenic agent, anti-cancer agent, alkaloid, blood pressure controlling agent, hormone, anti-inflammatory agent, muscle relaxant, steroid, soporific agent, anti-ischemic agent, anti-arrythmic agent, contraceptive, vitamin, mineral, tranquilizer, neurotransmitter regulating agent, wound and burn healing agent, anti-angiogenic agent, cytokine, growth factor, anti-metastatic agent, antacid, anti-histaminic agent, anti-bacterial agent, anti-viral agent, anti-gas agent, appetite suppressant, sun screen, emolient, skin temperature lowering product, radioactive phosphorescent or fluorescent contrast diagnostic or imaging agent, libido altering agent, bile acid, laxative, anti-diarrheic agent, skin renewal agent, hair growth agent, anti-menopausal agent such as hormone, nociceptic agent, other agents useful for the treatment of diseases associated or accompanied with pain and inflammation such as arthritis, burns, wounds, chronic bronchitis, chronic obstructive pulmonary disease, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, autoimmune disease such as lupus erythematosus, agent for reperfusion injury or counteracting appetite suppressant. P2 is a hormone selected from female and male sex hormone, **thyroxine** or glucocorticoid, sedative, selected from diphenhydramine, hydroxyzine, methotrimeprazine, promethazine, protofol, melatonin, trimeprazzine, amitriptyline HCl, chlordiazepoxide, amobarbital, secobarbital, aprobarbital, butabarbital, ethchiorvynol, glutethimide, L-tryptophan, mephobarbital, methohexital Na, midazolam HCl, oxazepam, pentobarbital Na, Phenobarbital, secobarbital Na or thiamylal Na; libido altering agent selected from Viagra or other NO-level modulating agent; analgesic selected from acetominophen, anilerdine, aspirin, buprenorphine, butabital, butorpphanol, choline salicylate, codeine, dezocine, diclofenac, diflunisal, dihydrocodeine, elcatoninin, etodolac, fenoprofen, hydrocodone, hydromorphone, ibuprofen, ketoprofen, ketorolac, levorphanol, magnesium salicylate, meclofenamate, mefenamic acid, meperidine, methadone, methotrimeprazine, morphine, nalbuphine, naproxen, opium, oxycodon, oxymorphone, pentazocine, Phenobarbital, propoxyphene, salicylic acid, tramadol, narcotic analgesic, ibuprofen, acetyl salicylate, oruda, aleve, acetaminofen or controlled substance selected from morphine or codeine; anti-depressant selected from tricyclics, MAO inhibitor or epinephrine, gamma-amino butyric acid, chlordiazepoxide, amitriptyline, loxapine maprotiline and perphenazine, dopamine or serotonin level elevating agent selected from prozac, amytryptilin, wellbutrin or Zoloft; skin renewal agent; hair growth agent; anti-anxiety agent selected from alprazolam, bromazepam, buspirone, chlordiazepoxide, chlormezanone, clorazepate, diazepam, halazepam, hydroxyzine, ketaszolam, lorazepam, meprobamate, oxazepam or prazepam; anti-inflammatory agent selected from non-steroidal anti-inflammatory drug, diclofenac, beclomethaxone, budesonide, dexamethasone, flunisolide, triamcinolone, flurbiprofen, indomethacin, ketorolac, rimexolone, non-rheumatic aspirin, choline salicylate, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin,

ketoprofen, magnesium salicylate, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozen, phenylbutazone, piroxicam, salsalate, sodium salicylate, sulindac, tenoxicam, tiaprofenic acid, tolmetin or glucocorticosteroid; soporific selected from melatonin, diazepam, cytoprotective, anti-ischemic , agent for the treatment of head injuries or alprazolam, bromozepam, diazepam, diphenylhydramine, doxylamine, estazolam, flurazepam, halazepam, ketazolam, lorazepam, nitrazepam, prazepam quazepam, temazepam, triazolam, zolpidem or sopiclone. P3 is a therapeutic or diagnostic agent for the treatment of brain injury/ischemia; cytoprotective agent and agent for the treatment of menopause or menopausal symptoms selected from ergotamine, belladonna alkaloid, Phenobarbital, clonidine, conjugated estrogen, medroxyprogesterone, estradiol, estradiol cypionate, estradiol valerate, estrogen, conjugated estrogen, esterified estrone, estropipate or ethinyl estradiol; agent for the treatment of symptoms of premenstrual syndrome selected from progesterone, progestin, gonadotrophic releasing hormone, oral contraceptive, danazol, luprolide acetate or vitamin B6; agent for the treatment of emotional/psychiatric symptoms selected from tricyclic anti-depressants selected from amitriptyline HCl (elavil), amitriptyline HCl, perphenazine (triavil) or doxepine HCl (sinequan), diazepam (valium), lorazepam (ativan), alprazolam (xanax), selective serotonin reuptake inhibitor, fluoxetine HCl (prozac), sertaline HCl (zoloft), paroxetine HCl (paxil), fluvoxamine maleate (luvox), venlafaxine HCl (effexor), serotonin, serotonin agonist (fenfluramine); or anti-migraine agent. Preferred Kit: (A1) is provided as inhalable, respirable, intrapulmonary or nasal formulation. The delivery device comprises an inhaler provided with an aerosol or aerosol or spray generator that delivers particles having a size of 0.05 - 10 micron in size or about 8 - 100 micron in size. The delivery device delivers individual pre-metered doses of (C1) and comprises an inhaler (preferably compression inhaler) and a nebulizer or insufflator. (A1) is provided as a formulation in a pierceable or openable capsule or cartridge.

L86 ANSWER 24 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-029845 [02] WPIX
CROSS REFERENCE: 2002-682712; 2003-278421; 2003-393354; 2003-697560
DOC. NO. CPI: C2003-006743 [02]
TITLE: Apparatus for transporting thyroid hormone drug formulations from blender to tableting machine comprises blender, portable container and conical tablet press inlet, useful for treatment of canine and feline hypothyroidism
DERWENT CLASS: A96; B05; B07
INVENTOR: DIMENNA P A; FRANZ G A; GEMMA R L; STRAUSS E A
PATENT ASSIGNEE: (KING-N) KING PHARM INC
COUNTRY COUNT: 97

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002067854	A2	20020906	(200302)*	EN	30[9]	A61K000-00
AU 2002258397	A1	20020912	(200420)	EN		
AU 2002240394	A1	20030909	(200469)	EN		A61K009-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002067854	A2	WO 2002-US4504	20020215

AU 2002240394 A1 AU 2002-240394 20020215
AU 2002258397 A1 AU 2002-258397 20020215

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002258397 A1	Based on	WO 2002067854 A
AU 2002240394 A1	Based on	WO 2003070217 A

PRIORITY APPLN. INFO: US 2001-268998P 20010215
US 2001-269009P 20010215
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A01N0037-12 [I,A]; A01N0037-12 [I,C]; A01N0037-44 [I,A]; A01N0037-44 [I,C]; A61K [I,S]; A61K0031-185 [I,C]; A61K0031-195 [I,A]; A61K0031-198 [I,A]; A61K0009-00 [I,A] ; A61K0009-00 [I,C]; A61K0009-20 [I,A]; A61K0009-20 [I,C] ; A61K0009-30 [I,C]; A61K0009-38 [I,A]; A61K0009-44 [I,A] ; A61K0009-44 [I,C]; B01F0003-00 [I,C]; B01F0003-18 [I,A] ; B01F0005-00 [I,C]; B01F0005-06 [I,A]; B01F0005-06 [I,C] ; B01F0005-24 [I,A]

BASIC ABSTRACT:

WO 2002067854 A2 UPAB: 20060118

NOVELTY - Apparatus for transporting thyroid hormone drug formulations from a blender to a tableting machine comprising a blender discharge section, portable container section, portable container discharge section and conical tablet press inlet section, where mass flow of the formulation is maintained in all sections, is new.

USE - The apparatus is useful for producing compositions for treating canine or feline hypothyroidism (claimed).

ADVANTAGE - The apparatus maintains consistent tablet composition during manufacture.

MANUAL CODE: CPI: A03-A00A; A12-V01; B04-C02A1; B04-C02B2; B04-D02; B04-N02; B05-A01B; B05-B02C; B07-A02A; B07-A02B; B10-B02B; B10-C04E; B11-C05; B11-C06; B12-M11; B14-N11; B14-S12

TECH

ORGANIC CHEMISTRY - Preferred Apparatus: The portable container discharge section is a vent cone optionally with a Y-branch section.

PHARMACEUTICALS - Preferred Formulation: The drug formulation contains one or more active agents selected from **levothyroxine sodium** and liothyronine sodium. The formulation is preferably liothyronine sodium, calcium sulfate, **gelatin**, starch, stearic acid, sucrose and talc, or **levothyroxine sodium**, lactose, microcrystalline cellulose, pregelatinized starch and magnesium stearate.

ORGANIC CHEMISTRY - Preferred Apparatus: The portable container discharge section is a vent cone optionally with a Y-branch section.

PHARMACEUTICALS - Preferred Formulation: The drug formulation contains one or more active agents selected from **levothyroxine sodium** and liothyronine sodium. The formulation is preferably liothyronine sodium, calcium sulfate, **gelatin**, starch, stearic acid, sucrose and talc, or **levothyroxine sodium**, lactose, microcrystalline cellulose, pregelatinized starch and magnesium stearate.

IT UPIT 20060118

99369-CL; 147062-CL; 95972-CL; 107779-CL; 90356-CL; 89852-CL; 2021-CL; 2853-CL; 108296-CL; 1092-CL

M2 *01* A111 A960 C710 G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M411 M424 M431 M510 M520 M532 M540 M630 M740 M782 N104 N105 P624 Q130 R038 M905 M904

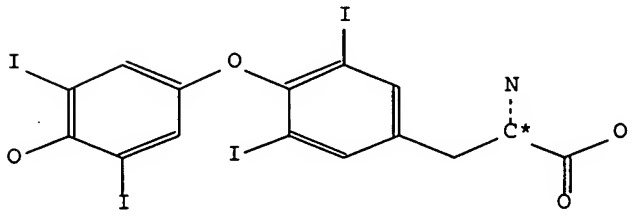
DCN: **RA11AM-K RA11AM-M RA11AM-T**
DCR: **99369-K 99369-M 99369-T**

AN.S DCR-99369
CN.P LEVOTHYROXINE SODIUM
CN.S 2-amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionate; Sodium
SDCN RA11AM

CM 1

Na

CM 2



L86 ANSWER 25 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-479585 [51] WPIX
CROSS REFERENCE: 2002-479584
DOC. NO. CPI: C2002-136439 [51]
TITLE: New drug dosage form useful as therapeutic agent comprises a compound susceptible to moisture-induced degradation and at least one excipient prepared under low compression
DERWENT CLASS: A96; B05
INVENTOR: SPIREAS S; SPIRIDON S
PATENT ASSIGNEE: (MUTU-N) MUTUAL PHARM CO INC; (SIGM-N) SIGMAPHARM INC
COUNTRY COUNT: 96

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002028365	A2	20020411	(200251)*	EN	25[0]	
AU 2001094735	A	20020415	(200254)	EN		
EP 1322295	A2	20030702	(200344)	EN		
CN 1617714	A	20050518	(200558)	ZH		A61K009-48
MX 2003002807	A1	20041101	(200558)	ES		
US 20050249801	A1	20051110	(200574)	EN		A61K009-48
US 6979462	B1	20051227	(200603)	EN		
NZ 524568	A	20051028	(200606)	EN		
AU 2001294735	B2	20060713	(200707)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

WO 2002028365 A2	WO 2001-US30093 20010926
US 20050249801 A1 Provisional	US 2000-237442P 20001003
US 6979462 B1 Provisional	US 2000-237442P 20001003
US 20050249801 A1 Cont of	US 2000-690974 20001018
US 6979462 B1	US 2000-690974 20001018
AU 2001094735 A	AU 2001-94735 20010926
CN 1617714 A	CN 2001-816398 20010926
EP 1322295 A2	EP 2001-975404 20010926
NZ 524568 A	NZ 2001-524568 20010926
EP 1322295 A2	WO 2001-US30093 20010926
MX 2003002807 A1	WO 2001-US30093 20010926
NZ 524568 A	WO 2001-US30093 20010926
MX 2003002807 A1	MX 2003-2807 20030331
US 20050249801 A1	US 2005-184341 20050719
AU 2001294735 B2	AU 2001-294735 20010926

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
AU 2001094735	A	Based on	WO 2002028365	A
EP 1322295	A2	Based on	WO 2002028365	A
MX 2003002807	A1	Based on	WO 2002028365	A
NZ 524568	A	Based on	WO 2002028365	A
AU 2001294735	B2	Based on	WO 2002028365	A

PRIORITY APPLN. INFO: US 2000-690974 20001018
US 2000-237442P 20001003
US 2005-184341 20050719

INT. PATENT CLASSIF.:
MAIN: A61K009-48
IPC ORIGINAL: A61K0009-00 [I,A]; A61K0009-20 [I,A]; A61K0009-48 [I,A]
IPC RECLASSIF.: A61K0009-20 [I,A]; A61K0009-20 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,C]

BASIC ABSTRACT:

WO 2002028365 A2 UPAB: 20060202

NOVELTY - A drug dosage form (I) comprises a compound susceptible to moisture-induced degradation and at least one excipient prepared under low compression.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a drug dosage form for a thyroid drug (preferably **levothyroxine**) comprises a compound susceptible to moisture-induced degradation mixed with either a non-volatile oil, an excipient mixed with non-volatile oil or at least one hydrophobic powder; and

(2) a drug dosage form (II) comprises a thyroid drug (preferably **levothyroxine**) mixed with oil together with a first excipient mixed with second oil.

ACTIVITY - Antithyroid.

MECHANISM OF ACTION - None given.

USE - As therapeutic agent in the treatment of disorders associated with reduction or absence of thyroid hormone production e.g. hypothyroidism, hypothyrosis, iodine deficiency and other related diseases.

ADVANTAGE - (I) shows improved stability to moisture-induced degradation of the hormone as compared with a tablet form of the hormone. (I) is subjected to compression not more than 10000 (preferably 5000, especially 2000) psi/g. (I) is stable and shows long shelf life for use as therapeutic agent. (I) improves stability of drugs such as **levothyroxine sodium**. (I) shows reduced degradation and hydrolysis. (I) shows reduced tendency to degrade over time when compared with traditional formulations of such drugs. MANUAL CODE: CPI: A99-A; B04-B01C; B04-C02A; B04-C02B; B05-A01B;

B05-A02; B10-B02J; B12-M11C; B14-N11

TECH PHARMACEUTICALS - Preferred Form: (I) comprises a capsule formed of hydroxypropyl methylcellulose. The compound is contained in solid form within a capsule.
Preferred Process: The hydrophobic powder of (V) is triturated directly with the compound. (I) is subjected to compression not more than 10000 (preferably 5000, especially 2000) psi/g.
POLYMERS - Preferred Components: The excipient is hydroxypropyl methylcellulose, carboxymethyl cellulose, microcrystalline cellulose, amorphous silicon dioxide, magnesium stearate, starch and/or sodium starch glycolate. The excipient has residual moisture content of less than about 10 wt.%.
ORGANIC CHEMISTRY - Preferred Components: The oil in (I), (II) and (III) is animal (e.g. vitamin E, fish or tallow-derived oil) or vegetable oil (e.g. olive, corn, peanut, nut, soy, rapeseed or cottonseed).
Preferred Form: The compound-oil mixture of (II) is present within a capsule (preferably soft-shell capsule or specially sealed hard-shell capsule). The hydrophobic powder is magnesium stearate. Preferred Process: At least some of the compound-oil mixture of (II) is adsorbed on an excipient. The excipient having the compound-oil mixture is adsorbed within a capsule or a tablet.
INORGANIC CHEMISTRY - Preferred Components: The oil in (I), (II) and (III) is mineral oil or silicone oil.

DETD DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) a drug dosage form for a thyroid drug (preferably **levothyroxine**) comprises a compound susceptible to moisture-induced degradation mixed with either a non-volatile oil, an excipient mixed with non-volatile oil or at least one hydrophobic powder; and
(2) a drug dosage form (II) comprises a thyroid drug (preferably **levothyroxine**) mixed with oil together with a first excipient mixed with second oil.

ADV ADVANTAGE - (I) shows improved stability to moisture-induced degradation of the hormone as compared with a tablet form of the hormone. (I) is subjected to compression not more than 10000 (preferably 5000, especially 2000) psi/g. (I) is stable and shows long shelf life for use as therapeutic agent. (I) improves stability of drugs such as **levothyroxine sodium**. (I) shows reduced degradation and hydrolysis. (I) shows reduced tendency to degrade over time when compared with traditional formulations of such drugs.

ABEX ADMINISTRATION - (I) is administered orally in form of a capsule (claimed).
EXAMPLE - A powder formulation (test) was prepared by pretreating excipient with oil. The formulation comprised of (mg/unit dose) **levothyroxine sodium** (0.025), soybean oil (2), acetone (40), Methocel K100M (hydroxypropyl methylcellulose) (10), Syloid 244 FP (amorphous silicon dioxide) (15), Avicel PH 200 (150). A first aliquot (1 kg) was compressed into a tablet. A second aliquot of the test was encapsulated in **gelatin** capsule. A third aliquot of each formulation was encapsulated in hard-shell HPMC capsules. Samples of each of the tablet and capsule was then stored at 60degreesC and a relative humidity of 75% for 4 - 6 days. Tablets of commercially available product synthroid (0.025 mg) were used as control. The % degradation was then determined. The results showed that the pretreated liquisolid powder system could be compressed into tablets and the tablets showed superior stability properties than the control product. It was observed that the test formulation when stored for 5 days at 60degreesC and 75% relative humidity, degraded at a level of only 14% whereas the control tablets displayed a 36.7% degradation at the same storage conditions.

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IT   UPIT 20060202
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     549683-CL; 202718-CL; 102715-CL; 91613-CL; 111074-CL; 107462-CL;
     105392-CL; 91676-CL; 184619-CL; 108879-CL; 107016-CL; 1092-CL
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          140011-U 140012-U 190069-U 90356-U
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               DCR: 133996-K 133996-M 134014-K 134014-M 97486-K 97486-M
     M1 *02*   H5 H521 H8 J0 J011 J1 J171 M280 M311 M321 M342 M381 M391 M423
               M431 M782 Q120 R031  M905 M904 M910
               DCN: R01835-K R01835-M R06717-K R06717-M
               DCR: 133912-K 133912-M 133912-U 133998-U 140011-U 140012-U
               190069-U
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               DCR: 107782-K 107782-M
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               DCN: RA07ZC-K RA07ZC-M
               DCR: 95167-K 95167-M
     M1 *07*   M423 M431 M782 Q120 R031  M905
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     M1 *09*   M423 M431 M782 Q120 R031  M905
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M905 M904 M910
DCN: **R00050-K R00050-M R00050-T**
R04769-K R04769-M R04769-T
DCR: **108879-K 108879-M 108879-T**
108879-U

M2 *17* B114 B702 B720 B831 C108 C800 C802 C803 C804 C805 C807 M411 M431
M782 Q120 R031 M905 M904
DCN: R01694-K R01694-M
DCR: 107016-K 107016-M 107016-U

M2 *18* A212 A960 C710 J0 J011 J1 J171 M225 M231 M262 M281 M320 M411
M431 M510 M520 M530 M540 M620 M630 M782 Q120 R031 M905 M904
DCN: R01376-K R01376-M
DCR: 1092-K 1092-M

DRN **0050-U** 1694-U 1835-U 1852-U 1863-U

M2 *16* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609
H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343
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DCN: **R00050-K R00050-M R00050-T**
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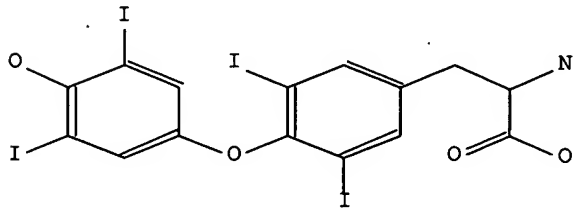
DCR: **108879-K 108879-M 108879-T**
108879-U

AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 26 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-479584 [51] WPIX
CROSS REFERENCE: 2002-479585
DOC. NO. CPI: C2002-136438 [51]
TITLE: New drug dosage form useful as therapeutic agent comprises thyroid hormone and at least one excipient prepared under low compression
DERWENT CLASS: A96; B05
INVENTOR: SPIREAS S
PATENT ASSIGNEE: (MUTU-N) MUTUAL PHARM CO INC; (SIGM-N) SIGMAPHARM INC
COUNTRY COUNT: 96

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

WO 2002028364	A2	20020411	(200251)*	EN	29[0]
AU 2001091244	A	20020415	(200254)	EN	
EP 1322294	A2	20030702	(200344)	EN	
NZ 524567	A	20041224	(200506)	EN	
US 6855333	B1	20050215	(200513)	EN	
CN 1543341	A	20041103	(200514)	ZH	A61K009-20
MX 2003002809	A1	20041101	(200558)	ES	
AU 2001291244	B2	20060921	(200712)	EN	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002028364	A2	WO 2001-US29986	20010926
US 6855333	B1 Provisional	US 2000-237442P	20001003
US 6855333	B1	US 2000-690973	20001018
AU 2001091244	A	AU 2001-91244	20010926
CN 1543341	A	CN 2001-816593	20010926
EP 1322294	A2	EP 2001-971348	20010926
NZ 524567	A	NZ 2001-524567	20010926
EP 1322294	A2	WO 2001-US29986	20010926
NZ 524567	A	WO 2001-US29986	20010926
MX 2003002809	A1	WO 2001-US29986	20010926
MX 2003002809	A1	MX 2003-2809	20030331
AU 2001291244	B2	AU 2001-291244	20010926

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
NZ 524567	A	Div in	NZ 535680	A
AU 2001091244	A	Based on	WO 2002028364	A
EP 1322294	A2	Based on	WO 2002028364	A
NZ 524567	A	Based on	WO 2002028364	A
MX 2003002809	A1	Based on	WO 2002028364	A
AU 2001291244	B2	Based on	WO 2002028364	A

PRIORITY APPLN. INFO: US 2000-690973 20001018
US 2000-237442P 20001003

INT. PATENT CLASSIF.:

IPC ORIGINAL: A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0009-00 [I,A] ; A61K0009-00 [I,C]; A61K0009-20 [I,A]; A61K0009-20 [I,C] ; A61K0009-48 [I,A]; A61K0009-48 [I,C]

IPC RECLASSIF.: A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0009-20 [I,A] ; A61K0009-20 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,C]

BASIC ABSTRACT:

WO 2002028364 A2 UPAB: 20060119

NOVELTY - A drug dosage form (I) comprises a thyroid hormone and at least one excipient prepared under low compression.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a drug dosage form for a thyroid drug (preferably **levothyroxine**) comprises the drug which is mixed with either a non-volatile oil, a excipient mixed with non-volatile oil or at least one hydrophobic powder; and

(2) a drug dosage form (II) comprises a thyroid drug (preferably **levothyroxine**) mixed with oil together with a first excipient mixed with second oil.

ACTIVITY - Antithyroid.

MECHANISM OF ACTION - None given.

USE - As therapeutic agent in the treatment of disorders associated with reduction or absence of thyroid hormone production e.g. hypothyroidism, hypothyrosis, iodine deficiency and other related diseases.

ADVANTAGE - (I) shows improved stability to moisture-induced degradation of the hormone as compared with a tablet form of the hormone. (I) is stable and shows long shelf life for use as therapeutic agent. (I) improves stability of drugs such as **levothyroxine sodium**. (I) shows reduced degradation and hydrolysis. (I) shows reduced tendency to degrade over time when compared with traditional formulations of such drugs.

MANUAL CODE: CPI: A99-A; B04-B01C; B04-C02A; B04-C02B; B05-A01B; B10-B02J; B12-M11C; B14-N11

TECH

PHARMACEUTICALS - Preferred Form: (I) comprises a capsule formed of hydroxypropyl methylcellulose. The hormone (preferably **levothyroxine**) is contained in solid form within a capsule.

Preferred Process: The hydrophobic powder of (III) is triturated directly with the thyroid hormone (preferably **levothyroxine**). (I) is subjected to compression not more than 10000 (preferably 5000, especially 2000) psi/g.

POLYMERS - Preferred Components: The excipient is hydroxypropyl methylcellulose, carboxymethyl cellulose, microcrystalline cellulose, amorphous silicon dioxide, magnesium stearate, starch and/or sodium starch glycolate. The excipient has residual moisture content of less than about 10 wt.%.

ORGANIC CHEMISTRY - Preferred Components: The oil in (I) and (II) is animal (e.g. vitamin E, fish or tallow-derived oil) or vegetable oil (e.g. olive, corn, peanut, nut, soy, rapeseed or cottonseed).

Preferred Form: The drug-oil mixture is present within the capsule (preferably soft shell capsule or specially sealed hard-shell capsule). The hydrophobic powder is magnesium stearate.

Preferred Process: At least some of the drug-oil mixture is adsorbed on an excipient. The excipient having the drug-oil mixture (preferably **levothyroxine**-oil mixture) is adsorbed within a capsule or a tablet. The **levothyroxine** is purified **levothyroxine**.

INORGANIC CHEMISTRY - Preferred Components: The oil in (I) and (II) is mineral oil or silicone oil.

DETD DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a drug dosage form for a thyroid drug (preferably **levothyroxine**) comprises the drug which is mixed with either a non-volatile oil, a excipient mixed with non-volatile oil or at least one hydrophobic powder; and

(2) a drug dosage form (II) comprises a thyroid drug (preferably **levothyroxine**) mixed with oil together with a first excipient mixed with second oil.

ADV ADVANTAGE - (I) shows improved stability to moisture-induced degradation of the hormone as compared with a tablet form of the hormone. (I) is stable and shows long shelf life for use as therapeutic agent. (I) improves stability of drugs such as **levothyroxine sodium** . (I) shows reduced degradation and hydrolysis. (I) shows reduced tendency to degrade over time when compared with traditional formulations of such drugs.

PHARMACEUTICALS - Preferred Form: (I) comprises a capsule formed of hydroxypropyl methylcellulose. The hormone (preferably **levothyroxine**) is contained in solid form within a capsule.

Preferred Process: The hydrophobic powder of (III) is triturated directly with the thyroid hormone (preferably **levothyroxine**). (I) is subjected to compression not more than 10000 (preferably 5000, especially 2000) psi/g.

POLYMERS - Preferred Components: The excipient is hydroxypropyl methylcellulose, carboxymethyl cellulose, microcrystalline cellulose,

amorphous silicon dioxide, magnesium stearate, starch and/or sodium starch glycolate. The excipient has residual moisture content of less than about 10 wt.%.

ORGANIC CHEMISTRY - Preferred Components: The oil in (I) and (II) is animal (e.g. vitamin E, fish or tallow-derived oil) or vegetable oil (e.g. olive, corn, peanut, nut, soy, rapeseed or cottonseed).

Preferred Form: The drug-oil mixture is present within the capsule (preferably soft shell capsule or specially sealed hard-shell capsule). The hydrophobic powder is magnesium stearate.

Preferred Process: At least some of the drug-oil mixture is adsorbed on an excipient. The excipient having the drug-oil mixture (preferably **levothyroxine**-oil mixture) is adsorbed within a capsule or a tablet. The **levothyroxine** is purified **levothyroxine.**

INORGANIC CHEMISTRY - Preferred Components: The oil in (I) and (II) is mineral oil or silicone oil.

ABEX ADMINISTRATION - (I) is administered to a patient as unit dose which has not been processed employing high compression admixed with a susbstantially non-volatile oil. (I) is administered orally in the form of a capsule (claimed).

EXAMPLE - A powder formulation (test) was prepared by pretreating excipient with oil. The formulation comprised of (mg/unit dose) **levothyroxine sodium** (0.025), soybean oil (2), acetone (40), Methocel K100M (hydroxypropyl methylcellulose) (10), Syloid 244 FP (amorphous silicon dioxide) (15), Avicel PH 200 (150). A first aliquot (1 kg) was compressed into a tablet. A second aliquot of the test was encapsulated in **gelatin** capsule. A third aliquot of each formulation was encapsulated in hard-shell HPMC capsules. Samples of each of the tablet and capsule was then stored at 60degreesC and a relative humidity of 75% for 4 - 6 days. Tablets of commercially available product synthroid (0.025 mg) were used as control. The % degradation was then determined. The results showed that the pretreated liquisolid powder system could be compressed into tablets and the tablets showed superior stability properties than the control product. It was observed that the test formulation when stored for 5 days at 60degreesC and 75% relative humidity, degraded at a level of only 14% whereas the control tablets displayed a 36.7% degradation at the same storage conditions.

IT UPIT 20060119

; 184619-CL; 97486-CL; 133912-CL; 90356-CL; 107779-CL; 107782-CL; 95167-CL; 202718-CL; 549683-CL; 102715-CL; 91613-CL; 111074-CL; 107462-CL; 105392-CL; 91676-CL; **108879-CL**; 1092-CL 1092-ST

CMC UPB 20060119

DRN: **0050-U** 1835-U 1852-U 1863-U

DCR: 107779-U **108879-U** 133912-U 133998-U 135415-U 140011-U 140012-U 190069-U 90356-U

M1 *01* M423 M431 M782 N103 Q120 R031 M905
DCN: RA08SW-K RA08SW-M
DCR: 184619-K 184619-M

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M1 *03* H5 H521 H8 J0 J011 J1 J171 M280 M311 M321 M342 M381 M391 M423 M431 M782 N103 Q120 R031 M905 M904 M910
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DCR: 133912-K 133912-M 133912-U 133998-U 140011-U 140012-U 190069-U

M1 *04* M423 M431 M782 N103 Q120 R031 M905 M904 M910
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DCR: 135415-U 90356-K 90356-M 90356-U

M1 *05* M423 M431 M782 N103 Q120 R031 M905 M904 M910

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                DCN: RA00CU-K RA00CU-M
                DCR: 107782-K 107782-M
      M1 *07*   H7 H723 J0 J011 J1 J171 M226 M231 M262 M281 M320 M416 M423 M431
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                DCR: 95167-K 95167-M
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      M1 *09*   M423 M431 M782 N103 Q120 R031  M905
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                M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 N103 P624 Q120
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                R04769-K R04769-M R04769-T
                DCR: 108879-K 108879-M 108879-T
                108879-U
AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic
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SDCN R00050; R04769
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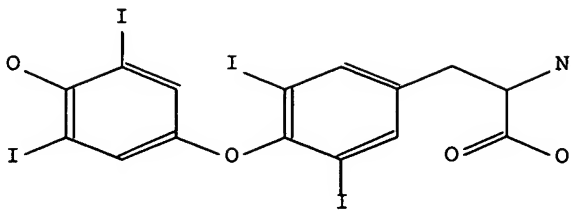
SDRN 0050



L86 ANSWER 27 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-526093 [48] WPIX
CROSS REFERENCE: 1996-300361
DOC. NO. CPI: C1997-167291 [48]
DOC. NO. NON-CPI: N1997-438476 [48]
TITLE: Encapsulation of caplets in a capsule by cold shrinking - in cost-effective process, used for foodstuffs, dyestuffs, pharmaceuticals and agrochemicals, is tamper-proof and more acceptable than prior art
DERWENT CLASS: A11; A14; A96; B07; C07; D13; J04; P33
INVENTOR: AMEY J; CADE D; MAES P; SCOTT R; SCOTT R A
PATENT ASSIGNEE: (WARN-C) WARNER LAMBERT CO; (WARN-C) WARNER LAMBERT CO LLC
COUNTRY COUNT: 31

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9737629	A1	19971016	(199748)*	EN	24[0]	
EP 891180	A1	19990120	(199908)	EN		
CA 2214923	A1	19990309	(199934)#	EN		
CN 1215322	A	19990428	(199935)	ZH		A61J003-07
JP 2000508552	W	20000711	(200038)	JA	22	A61J003-07
KR 2000005232	A	20000125	(200061)	KO		
MX 9807667	A1	19990801	(200063)	ES		A61J003-07
US 6245350	B1	20010612	(200135)	EN		
EP 891180	B1	20020703	(200243)	EN		
DE 69713757	E	20020808	(200259)	DE		
ES 2175388	T3	20021116	(200302)	ES		
PH 1199756054	B1	20030805	(200512)	EN		A61K009-48
CN 1123333	C	20031008	(200553)	ZH		
KR 463356	B	20050516	(200657)	KO		A61J003-07
MX 239306	B	20060804	(200702)	ES		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9737629 A1		WO 1997-US4482	19970324
US 6245350 B1	Cont of	US 1994-358137	19941216
US 6245350 B1	CIP of	US 1996-585549	19960111
US 6245350 B1		US 1996-628823	19960405
CN 1215322 A		CN 1997-193572	19970324

CN 1123333 C	CN 1997-193572 19970324
DE 69713757 E	DE 1997-613757 19970324
EP 891180 A1	EP 1997-916858 19970324
EP 891180 B1	EP 1997-916858 19970324
DE 69713757 E	EP 1997-916858 19970324
ES 2175388 T3	EP 1997-916858 19970324
JP 2000508552 W	JP 1997-536220 19970324
EP 891180 A1	WO 1997-US4482 19970324
JP 2000508552 W	WO 1997-US4482 19970324
KR 2000005232 A	WO 1997-US4482 19970324
EP 891180 B1	WO 1997-US4482 19970324
DE 69713757 E	WO 1997-US4482 19970324
KR 463356 B	WO 1997-US4482 19970324
PH 1199756054 B1	PH 1997-56054 19970403
CA 2214923 A1	CA 1997-2214923 19970909
MX 9807667 A1	MX 1998-7667 19980921
KR 2000005232 A	KR 1998-707919 19981002
KR 463356 B	KR 1998-707919 19981002
MX 239306 B	WO 1997-US4482 19970324
MX 239306 B	MX 1998-7667 19980921

FILING DETAILS:

PATENT NO	KIND		PATENT NO	
DE 69713757	E	Based on	EP 891180	A
ES 2175388	T3	Based on	EP 891180	A
KR 463356	B	Previous Publ	KR 2000005232	A
US 6245350	B1	CIP of	US 6080426	A
EP 891180	A1	Based on	WO 9737629	A
JP 2000508552	W	Based on	WO 9737629	A
KR 2000005232	A	Based on	WO 9737629	A
EP 891180	B1	Based on	WO 9737629	A
DE 69713757	E	Based on	WO 9737629	A
KR 463356	B	Based on	WO 9737629	A
MX 239306	B	Based on	WO 9737629	A

PRIORITY APPLN. INFO: US 1996-628823 19960405
US 1994-358137 19941216
US 1996-585549 19960111
WO 1997-US4482 19970324
CA 1997-2214923 19970909

INT. PATENT CLASSIF.:
MAIN: A61J003-07; A61K009-48
SECONDARY: A61K009-38
IPC RECLASSIF.: A61J0003-07 [I,A]; A61J0003-07 [I,C]; A61K0009-20 [I,A]; A61K0009-20 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,C]

BASIC ABSTRACT:

WO 1997037629 A1 UPAB: 20060113 Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 weight%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-

60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.
USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.
ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided. MANUAL CODE: CPI: A12-V01; A12-W05; B04-C03B; B12-M11C; C04-C03B;
C12-M11C; D03-H01S; J04-A06

Member(0002)
ABEQ EP 891180 A1 UPAB 20060113
Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.
USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.
ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

Member(0004)
ABEQ CN 1215322 A UPAB 20060113
Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin**

capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

Member(0005)
ABEQ JP 2000508552 W UPAB 20060113

Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

Member(0008)
ABEQ US 6245350 B1 UPAB 20060113

Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to

pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

ALE Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

ABDT WO1997037629

Process for encapsulation of caplets in a capsule comprises:
(a) providing empty first and second capsule shell parts;
(b) filling at least one of the parts with one or more caplets;
(c) putting the capsule parts together; and
(d) treating the combined capsule parts by cold shrinking.
The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are re-humidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C.
Solid dosage forms obtained by the above process are claimed per se.
Also claimed is a process for filling hard gelatin capsules.
USE
The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.
ADVANTAGE
Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.
EXAMPLE
None given. (KKG)
PREFERRED PROCESS
The capsule parts are made from a hydrophilic polymer, with optional plasticiser(s) in amounts up to 40%, lubricant(s), colouring(s) in amount

up to 10%, and extenders up to 95%. A coating may also be included.
Polymer materials are gelatin, phthalated or succinated gelatin, starch, casein, chitosan, soya bean or safflower protein, alginates, xanthan or gellan gum, carrageenan, cellulose phthalate/acetate, polyvinyl acetate, hydroxypropylmethyl cellulose, polyvinyl acetate/phthalate, acrylic or methacrylic ester polymers, or mixtures of the above.
Plasticisers are polyethylene glycol, glycerol or its mono-, di-, or tri-acetates, sorbitol, dioctyl sodium sulphosuccinate, triethyl or tributyl citrate and/or 1,2-propanediol.
Lubricants are stearates of aluminium, calcium, magnesium, or tin, talc, sodium lauryl sulphate, lecithins, mineral oils, stearic acid and/or silicones.
The encapsulated pharmaceutical is betamethasone, thioctic acid, sotalol, salbutamol, norfenefrine, silymarin, dihydroergotamine, buflomedil, etofibrate, indomethacin, oxazepam, acetyl-digitoxins, piroxicam, haloperidol, isosorbide mononitrate, amitriptyline, diclofenac, nifedipine, verapamil, pyritinol, nitrendipene, doxycycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levo-thyroxine, tamoxifen, methyl-digoxin, O-(β-hydroxyethyl)-rutoside, propicillin, acyclovir mononitrate, paracetamolol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, 1-thyroxin, tramadol, bromocriptine, loperamide, ketofinen, fenoterol, ca-dobesilate, propranolol, minocycline, nicergoline, ambroxol, metoprolol, β-sitosterin, enalapril hydrogen maleate, bezafibrate, isosorbide dinitrate, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, despanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethyl-penicillin, furosemide, bromazepam, flunarizine, erythromycin, metoclopramide, acemetacin, ranitidine, biperiden, metamizol, doxepin, dipotassium chlorazepat, tetrazepam, oestramustine phosphate, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamid, cefaclor, etilefrin, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainide, Mg-pyridoxal-5-phosphate glutaminate, hymechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsidomine, glibornuride, dimethindene, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepid, kallidinogenase, oxyfedrine, baclofen, carboxymethyl-cystein, thioredoxin, β-hystine, 1-tryptophan, myrtol, bromelain, prenylamine, salazosulfapyridine, astemizole, sulpiride, benzerazid, dibenzepin, acetylsalicylic acid, miconazole, nystatin, ketoconazole, sodium picosulphate, colestyramate, gemfibrozil, rifampin, fluocortolone, mexiletine, amoxicillin, terfenadine, mucopolysaccharide-polysulphuric acid, triazolam, mianserin, tiaprofensaure, amezinium.methylsulphate, mefloquine, probucol, quinidine, carbamazepine, Mg-1-aspartate, penbutolol, piretanide, amitriptyline, caproteron, sodium valproinate, mebeverine, bisacodyl, 5-amino-salicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofine, estriol, nadolol, levo-mepromazine, doxorubicin, medofenoxat, azathioprine, flutamide, norfloxacin, fendiline, prajmalium-bitartrate, aescin acromycin, anipamil, benzocaine, β-carotene, chloramphenicol, chlorodiazepoxid, chlormadinone-acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, dicumarol, digoxin, drotaverine, gramicidine, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydroflumethiazide, ketoprofen, lonetil, medazepam, mefruside, methandrostenolone, sulfaperine, nalidixic acid, nitrazepam, nitrofurantoin, oestradiol, papaverine, phenacetin, phenobarbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactine, streptomycin, sulfamethizole, sulfamethazine, sulfamethoxoazole, sulfamethoxydiazinon, sulfathiazole, sulfisoxazole, testosterone,

tolazamide, tolbutamide, trimethoprim and/or tyrothricin.
Pharmaceutically acceptable colourings are quinophthalone, triphenylmethane, or xanthene dyes, iron oxides or hydroxides, titanium dioxide and/or natural dyes; specific colours are sunset yellow, allura red, amaranth, cochineal red, azogeranine, tartrazine, brilliant black, canthaxanthin, patent blue, fast green, brilliant blue, acid green, erythrosine, quinoline yellow, indigotin, curcumin, and carbon black.
Extenders are sunflower, soybean, cottonseed, peanut, or rapeseed proteins, lactose, gum arabic, acrylates or methacrylates, cellulose acetate/phthalate, hydroxypropyl methylcellulose and its phthalate, hydroxymethyl-cellulose, polyvinyl pyrrolidone, shellac, bentonite, polyvinyl acetate/phthalate, phthalated or succinated gelatin, agar-agar and/or hydroxyalkyl starches.
Coatings are cellulose acetate/phthalate, polyvinyl acetate/phthalate, methacrylic acid polymer, hypromellose phthalate and/or hydroxyalkyl methylcellulose phthalate.
In processing, the capsule material moisture content w/w is 15-18% (especially 16-18%).
The caplet is a compressed material, with conical ends for easy insertion, and has a clearance between capsule and caplet of 0 and -0.5 mm (i.e., the caplet is compressed in the capsule). The caplet may have a preformed step or groove so that the dosage unit can be divided. For filling, the capsule parts are maintained at RH of 60-80% for feeding in and filling. Better contact between caplet and capsule can be obtained by treating both contact surfaces with an adhesive, e.g., tackidex or aqueous gelatin, immediately before assembly, e.g., by spraying.
The assembled product is dried at 15-40°C (preferably 18-25°C). A film coating, e.g., enteric, may then be applied.

Member(0002)
ABEQ EP 891180 A1 UPAB 20060113
Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

Member(0004)
ABEQ CN 1215322 A UPAB 20060113

Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

Member(0005)
ABEQ JP 2000508552 W UPAB 20060113

Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

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Member(0008)
ABEQ US 6245350 B1 UPAB 20060113

Process for encapsulation of caplets in a capsule comprises: (a) providing empty first and second capsule shell parts; (b) filling at least one of

the parts with one or more caplets; (c) putting the capsule parts together; and (d) treating the combined capsule parts by cold shrinking. The parts for (a) are kept after production in humid conditions in the range 40-90% relative humidity (RH), to retain a moisture content in the range of 14-19% of the shell (or are rehumidified to this moisture content), before feeding into a capsule filling machine. The part is kept under humid conditions within the machine at the above moisture content, during rectifying and assembling with a caplet having a moisture content in the range 0-12 wt.%. The second capsule part is processed in the same manner. The encapsulated dosage form is dried at 20-40% RH and temperature 15-60°C. Solid dosage forms obtained by the above process are claimed per se. Also claimed is a process for filling hard **gelatin** capsules.

USE - The process provides solid dosage forms, and is applicable to pharmaceuticals, agrochemicals, foodstuffs and dyestuffs. The capsule shell halves optionally may not cover the caplet completely, providing possibilities for fast and slow release. Each half of the capsule can have the same or different colours; the caplet also may have a different colour.

ADVANTAGE - Capsule forms are easier to swallow. The capsule coating also has a neutral taste, in contrast to some medications, which may taste bitter and be refused, particularly by children. The product is also tamper-proof. The process is easy and cost-effective, and disadvantages of prior art attempts to solve the problem are avoided.

L86 ANSWER 28 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-086657 [08] WPIX
CROSS REFERENCE: 1993-100651; 1995-381884
DOC. NO. CPI: C1997-028135 [08]
TITLE: Treatment of skin wounds - using, e.g., gel formulations comprising a non-steroidal anabolic hormone in a nutrient medium such as MCDB 153
DERWENT CLASS: A96; B05
INVENTOR: LINDENBAUM E
PATENT ASSIGNEE: (LIFE-N) LIFE MEDICAL SCI INC
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 5591709	A	19970107	(199708)*	EN	31[15]	A61K009-06

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 5591709	A Cont of	US 1991-752849	19910830
US 5591709	A CIP of	US 1992-937486	19920828
US 5591709	A CIP of	US 1993-25216	19930302
US 5591709	A CIP of	US 1993-158808	19931129
US 5591709	A	US 1995-374944	19950118

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 5591709	A CIP of	US 5461030 A

PRIORITY APPLN. INFO: US 1995-374944 19950118

US 1991-752849 19910830
US 1992-937486 19920828
US 1993-25216 19930302
US 1993-158808 19931129

INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0031-545 [I,A]; A61K0031-545 [I,C]; A61K0031-57 [I,A] ; A61K0031-57 [I,C]; A61K0031-65 [I,A]; A61K0031-65 [I,C] ; A61K0038-18 [I,A]; A61K0038-18 [I,C]; A61K0038-27 [I,A] ; A61K0038-27 [I,C]; A61K0038-28 [I,A]; A61K0038-28 [I,C] ; A61K0038-40 [I,A]; A61K0038-40 [I,C]; A61L0026-00 [I,A] ; A61L0026-00 [I,C]

BASIC ABSTRACT:

US 5591709 A UPAB: 20050515 The following are claimed: (A) treatment of skin wounds, comprising applying to the skin wound a formulation comprising a mixture of non-steroidal anabolic hormones (including insulin (at a concentration of 500 ng/ml to 100 µg/ml), growth hormone (at a concentration of 0.5-20 ng/ml) and triiodothyronine or **thyroxine**) in MCDB 153 nutrient medium; the formulation also comprises an amount of agarose, **gelatin**, collagen or a hydrophilic cellulose polymer effective to produce a gel for delivery to the wound; (B) wound treatment gel formulation comprising amts. of at least two non-steroidal anabolic hormones (selected from insulin, growth hormone, triiodothyronine and **thyroxine**) effective to enhance healing of skin wounds in animals in combination with a cellular nutrient medium, which comprises essential amino acids, non-essential amino acids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose, in amts. effective to enhance the healing of the wound in combination with the anabolic hormones; the formulation also includes water and at least one polymer selected from polyhydroxyethylmethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, sepharose, agarose, collagen, cellulose, dextran, polyethyleneoxide, dextran-polyethylene, polyacrylamide, amylose and/or a hydrophilic cellulose polymer in amts. effective to form a gel for application of the formulation to the wound; and (C) treatment of skin wounds in animals comprising application of a formulation comprising an amount of a non-steroidal anabolic hormone (selected from insulin, triiodothyronine and/or **thyroxine**) effective to enhance healing of skin wounds in animals in combination with a nutrient medium (which comprises essential amino acids, non-essential amino acids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose) in amts. effective to enhance the healing of the wound in combination with the anabolic hormone.

USE - The processes/compsns. may be used for promoting wound healing of skin and related tissues.

ADVANTAGE - The nutrient medium functions with the hormone to promote the normal processes of elaboration, growth and healing of the wound and adjacent skin areas. The medium also serves to maintain a moist environment surrounding the wound area. MANUAL CODE: CPI: A03-A01; A12-V; A12-V01; B03-B; B03-C; B03-D; B04-C02; B04-C03; B04-J03A; B04-J05; B04-N02; B05-A01A; B05-A01B; B05-C07; B06-D09; B07-D04C; B10-A07; B10-B02E; B10-C04D; B12-M03; B14-D01; B14-N17B

ALE The following are claimed: (A) treatment of skin wounds, comprising applying to the skin wound a formulation comprising a mixture of non-steroidal anabolic hormones (including insulin (at a concentration of 500 ng/ml to 100 µg/ml), growth hormone (at a concentration of 0.5-20 ng/ml) and triiodothyronine or **thyroxine**) in MCDB 153 nutrient medium; the formulation also comprises an amount of agarose, **gelatin**, collagen or a hydrophilic cellulose polymer effective to produce a gel for delivery to the wound; (B) wound treatment gel formulation comprising amts. of at

least two non-steroidal anabolic hormones (selected from insulin, growth hormone, triiodothyronine and **thyroxine**) effective to enhance healing of skin wounds in animals in combination with a cellular nutrient medium, which comprises essential amino acids, non-essential amino acids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose, in amts. effective to enhance the healing of the wound in combination with the anabolic hormones; the formulation also includes water and at least one polymer selected from polyhydroxyethylmethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, sepharose, agarose, collagen, cellulose, dextran, polyethyleneoxide, dextran-polyethylene, polyacrylamide, amylose and/or a hydrophilic cellulose polymer in amts. effective to form a gel for application of the formulation to the wound; and (C) treatment of skin wounds in animals comprising application of a formulation comprising an amount of a non-steroidal anabolic hormone (selected from insulin, triiodothyronine and/or **thyroxine**) effective to enhance healing of skin wounds in animals in combination with a nutrient medium (which comprises essential amino acids, non-essential amino acids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose) in amts. effective to enhance the healing of the wound in combination with the anabolic hormone.

ABDT US5591709

The following are claimed:

(A) treatment of skin wounds, comprising applying to the skin wound a formulation comprising a mixture of non-steroidal anabolic hormones (including insulin (at a concentration of 500 ng/ml to 100 µg/ml), growth hormone (at a concentration of 0.5-20 ng/ml) and triiodothyronine or thyroxine)

in MCDB 153 nutrient medium; the formulation also comprising an amount of agarose, gelatin, collagen or a hydrophilic cellulose polymer effective to produce a gel for delivery to the wound;

(B) wound treatment gel formulation comprising amts. of at least two non-steroidal anabolic hormones (selected from insulin, growth hormone, triiodothyronine and thyroxine) effective to enhance healing of skin wounds in animals in combination with a cellular nutrient medium, which comprises essential aminoacids, non-essential aminoacids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose, in amts. effective to enhance the healing of the wound in combination with the anabolic hormones; the formulation also includes water and at least one polymer selected from polyhydroxyethylmethacrylate, polyvinylpyrrolidone, polyethylene glycol, gelatin, sepharose, agarose, collagen, cellulose, dextran, polyethyleneoxide, dextran-polyethylene, polyacrylamide, amylose and/or a hydrophilic cellulose polymer in amts. effective to form a gel for application of the formulation to the wound; and

(C) treatment of skin wounds in animals comprising application of a formulation comprising an amount of a non-steroidal anabolic hormone (selected from insulin, triiodothyronine and/or thyroxine) effective to enhance healing of skin wounds in animals in combination with a nutrient medium (which comprises essential aminoacids, non-essential amino acids, a mixture of vitamins (comprising amts. of folate, niacinamide, pantothenate, pyridoxine, riboflavin and thiamine), a mixture of inorganic ions (comprising calcium, sodium, potassium, magnesium and chloride) and glucose) in amts. effective to enhance the healing of the wound in combination with the anabolic hormone.

USE
The processes and compsns. may be used for promoting wound-healing of skin and related tissues.
ADVANTAGE
The nutrient medium functions with the hormone to promote the normal processes of elaboration, growth and healing of the wound and adjacent skin areas. The medium also serves to maintain a moist environment surrounding the wound area.
EXAMPLE
100g lyophilised powder of MCDB 153 was reconstituted with distilled, sterilised water and supplemented with human growth hormone to a final concentration of 0.5-2 ng/ml by conventional stirring. An amount of insulin-transferrin was added to a final concentration of 5 µg/ml. About 1 weight% of gelatin or collagen was added to provide a gel prod. for final delivery to wounds. (KKG)
PREFERRED MATERIALS
The nutrient medium is a serum-free nutrient medium selected from F10, F12, RPMI 1640, Basal Medium Eagle including Earle's salt base, serum free Dulbecco's Modified Eagle Medium, McCoy's 5A medium, MCDB 153, Medium 199 including Earle's salt base, Medium 199 including Hank's salt base, Minimal Essential Medium Eagle including Hank's salt base or Minimal Essential Medium Eagle including Earle's salt base.
The formulations may also comprise cellular growth factors or transforming growth factors.

IT UPIT 20050515
1013-CMP 1013-RCT 1013-RCT 1013-USE; 10240-DIS; 103217-CMP 103217-USE; 105093-CMP 105093-USE; 105627-CMP 105627-USE; 107305-CMP; 107779-CMP 107779-USE; 108739-USE; **108879-CMP 108879-USE**; 112-CMP; 128-CMP; 130597-CMP; 132205-USE; 133116-USE; 133961-USE; 135415-USE; 150704-USE; 152166-USE; 155304-USE; 159573-CMP; 189863-USE; 2358-CMP 2358-USE; 2409-CMP 2409-USE; 269-CMP; 303-CMP 303-USE; 444-DIS; 75344-CMP 75344-RCT 75344-RCT 75344-USE; 86729-CMP; 8781-CMP 8781-RCT 8781-RCT 8781-USE; 89842-USE; 900-CMP 900-USE; 90356-CMP 90356-USE; 91481-CMP; 92818-CMP 92818-USE; 95503-CMP 95503-USE; 95972-CMP; 99443-CMP 99443-USE

CMC UPB 20050515
DRN: 0038-U **0050-U** 0183-U 0185-U 0252-U 0326-S 0326-U 0444-S 0444-U 0467-U 0503-U 0546-S 0546-U 0678-U 1653-U 1852-U 1857-U 1863-U 2044-U
DCR: 1013-S 1013-U 103217-U 105093-U 105627-U 107779-U 108739-U **108879-U** 132205-U 133116-U 133961-U 135415-U 150704-U 152166-U 155304-U 189863-U 2358-U 2409-U 303-U 75344-S 75344-U 8781-S 8781-U 89842-U 900-U 90356-U 92818-U 95503-U 99443-U
M1 *15* J0 J011 J2 J221 J5 J581 K0 K4 K421 L5 L560 M210 M211 M262 M280 M281 M320 M423 M431 M782 P942 Q110 Q120 Q130 Q140 V734 M903 M904
DCN: R24070-M
DCR: 86729-M
M1 *16* M423 M431 M782 P942 Q110 Q120 Q130 Q140 V711 M903 M904 M910
DCN: R01852-M
DCR: 135415-U 90356-M 90356-U
M1 *17* M423 M431 M782 P942 Q110 Q120 Q130 Q140 V752 M903 M904
DCN: R24034-M
DCR: 91481-M
M1 *18* M423 M431 M782 P942 Q110 Q120 Q130 Q140 V721 M903 M904 M910
DCN: R01857-M
DCR: 92818-M 92818-U
M1 *19* M423 M431 M782 P942 Q110 Q120 Q130 Q140 V751 M903 M904
DCN: R24033-M
DCR: 95972-M

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M1 *20*   H4 H402 H482 H5 H589 H8 M280 M312 M323 M332 M342 M383 M393 M423
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          M903 M904 M910
          DCN: R02044-M
          DCR: 900-M 900-U
M1 *21*   M423 M431 M782 P942 Q110 Q120 Q130 Q140 V723  M903 M904 M910
          DCN: R01863-M
          DCR: 107779-M 107779-U
M1 *22*   H7 H714 H721 J0 J011 J3 J371 M210 M212 M262 M281 M320 M416 M423
          M431 M782 P942 Q110 Q120 Q130 Q140 V743  M903 M904 M910
          DCN: R00444-M R00444-Q
          DCR: 8781-M 8781-Q 8781-S 8781-U
M1 *23*   H7 H721 M210 M212 M320 M416 M423 M431 M610 M782 P942 Q110 Q120
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          DCN: R00326-M R00326-Q
          DCR: 1013-M 1013-Q 1013-S 1013-U
M1 *24*   F011 F012 F423 H2 H211 H7 H713 H721 J5 J521 L9 L941 M210 M212
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          Q120 Q130 Q140 V743  M903 M904
          DCN: R00546-M R00546-Q
          DCR: 75344-M 75344-Q 75344-S 75344-U
M2 *01*   A220 C810 M411 M431 M782 P942 Q110 Q120 Q130 Q140  M903 M904
          DCN: R03033-M
          DCR: 269-M
M2 *02*   C017 C100 C720 C730 C801 C803 C804 C805 C806 C807 M411 M417 M431
          M782 P942 Q110 Q120 Q130 Q140  M903 M904
          DCN: R06671-M
          DCR: 130597-M
M2 *03*   D012 D013 D940 G013 G100 H1 H100 H102 H121 H141 J0 J013 J1 J172
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          M373 M381 M391 M412 M431 M511 M520 M531 M540 M782 P942 Q110 Q120
          Q130 Q140  M903 M904 M910
          DCN: R00183-M
          DCR: 189863-U 95503-M 95503-U
M2 *04*   H4 H405 H484 H8 J4 J471 K0 L8 L814 L821 L831 M280 M315 M321 M332
          M344 M349 M381 M391 M416 M431 M620 M782 P942 Q110 Q120 Q130 Q140
          M903 M904 M910
          DCN: R00038-M
          DCR: 159573-M 303-M 303-U
M2 *05*   A212 C810 M411 M431 M782 P942 Q110 Q120 Q130 Q140  M903 M904
          DCN: R05247-M
          DCR: 128-M
M2 *06*   F013 F431 J0 J011 J3 J311 M280 M320 M413 M431 M510 M521 M530
          M540 M782 P942 Q110 Q120 Q130 Q140  M903 M904 M910
          DCN: R00678-M
          DCR: 2358-M 2358-U
M2 *07*   H4 H402 H482 H8 J0 J012 J1 J171 J3 J371 M280 M312 M315 M321 M332
          M333 M342 M343 M349 M381 M392 M416 M431 M620 M630 M640 M650 M782
          P942 Q110 Q120 Q130 Q140  M903 M904 M910
          DCN: R04995-M
          DCR: 103217-M 103217-U 133116-U 150704-U 89842-U
M2 *08*   A119 C810 M411 M431 M782 P942 Q110 Q120 Q130 Q140  M903 M904
          DCN: R03587-M
          DCR: 112-M
M2 *09*   F012 F013 F014 F015 F432 H4 H402 H482 H8 J5 J521 M210 M211 M240
          M281 M311 M322 M342 M373 M392 M413 M431 M510 M521 M530 M540 M782
          P942 Q110 Q120 Q130 Q140 V0 V323  M903 M904 M910
          DCN: R00252-M
          DCR: 105093-M 105093-U 152166-U
M2 *10*   D011 D013 D023 E270 H1 H181 H2 H201 H4 H404 H484 H8 J5 J522 K0
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L8 L812 L821 L833 L834 L9 L910 M210 M211 M240 M282 M315 M321 M332 M344 M383 M391 M412 M431 M511 M520 M530 M540 M782 P942 Q110 Q120 Q130 Q140 V0 V322 M903 M904 M910
DCN: R00503-M
DCR: 105627-M 105627-U 133961-U

M2 *11* A111 C810 M411 M431 M782 P942 Q110 Q120 Q130 Q140 M903 M904
DCN: R03586-M
DCR: 107305-M

M2 *12* F012 F013 F014 F015 F019 F541 F710 H1 H100 H121 H4 H401 H481 H8 K0 L7 L721 L9 L943 M210 M211 M240 M282 M311 M312 M321 M332 M342 M373 M392 M413 M431 M510 M522 M530 M540 M782 P942 Q110 Q120 Q130 Q140 V0 V321 M903 M904 M910
DCN: R00185-M
DCR: 108739-U 132205-U 155304-U 2409-M 2409-U

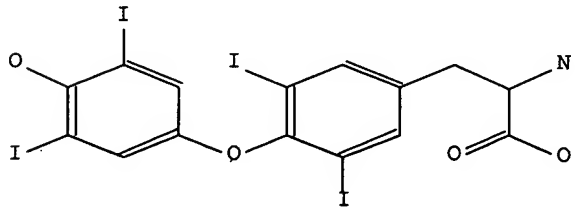
M2 *13* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P942 Q110 Q120 Q130 Q140 M903 M904 M910
DCN: **R00050-M**
DCR: **108879-M 108879-U**

M2 *14* G015 G017 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P942 Q110 Q120 Q130 Q140 M903 M904 M910
DCN: R01653-M
DCR: 99443-M 99443-U

DRN 0038-U **0050-U** 0183-U 0185-U 0252-U 0326-S 0326-U 0444-S 0444-U 0467-U 0503-U 0546-S 0546-U 0678-U 1653-U 1852-U 1857-U 1863-U 2044-U

M2 *13* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 P942 Q110 Q120 Q130 Q140 M903 M904 M910
DCN: **R00050-M**
DCR: **108879-M 108879-U**

AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 29 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-246488 [23] WPIX
DOC. NO. CPI: C1997-080054 [23]

TITLE: Stable thyroid hormone-containing compositions - comprise sodium thiosulphate as stabilising component, useful for treating thyroid diseases, particularly in e.g. thyroid over- and under-production

DERWENT CLASS: B05

INVENTOR: FRIESE A; LAHR W; WEICKGENANNT G

PATENT ASSIGNEE: (HENN-N) HENNING BERLIN GMBH; (HENN-N) HENNING BERLIN GMBH & CO; (LAHR-I) LAHR W; (SNFI-C) SANOFI SYNTHELABO GMBH

COUNTRY COUNT: 72

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
DE 19541128	A1	19970430	(199723)*	DE	5[0]	A61K047-04
WO 9716178	A1	19970509	(199724)	DE	17[0]	A61K031-195
AU 9672170	A	19970522	(199739)	EN		A61K031-195
DE 19541128	C2	19971127	(199751)	DE		A61K047-04
EP 857064	A1	19980812	(199836)	DE		A61K031-195
US 5958979	A	19990928	(199947)	EN		A61K031-195
JP 11514629	W	19991214	(200009)	JA	14	A61K031-195
EP 857064	B1	20021127	(200279)	DE		A61K031-195
DE 59609926	G	20030109	(200305)	DE		A61K031-195
ES 2185805	T3	20030501	(200341)	ES		A61K031-195

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
DE 19541128	A1	DE 1995-19541128	19951027
AU 9672170	A	AU 1996-72170	19960930
DE 59609926	G	DE 1996-59609926	19960930
EP 857064	A1	EP 1996-933433	19960930
EP 857064	B1	EP 1996-933433	19960930
DE 59609926	G	EP 1996-933433	19960930
ES 2185805	T3	EP 1996-933433	19960930
WO 9716178	A1	WO 1996-EP4274	19960930
EP 857064	A1	WO 1996-EP4274	19960930
US 5958979	A	WO 1996-EP4274	19960930
JP 11514629	W	WO 1996-EP4274	19960930
EP 857064	B1	WO 1996-EP4274	19960930
DE 59609926	G	WO 1996-EP4274	19960930
JP 11514629	W	JP 1997-517016	19960930
US 5958979	A	US 1998-51376	19980408

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DE 59609926	G Based on	EP 857064 A
ES 2185805	T3 Based on	EP 857064 A
AU 9672170	A Based on	WO 9716178 A
EP 857064	A1 Based on	WO 9716178 A
US 5958979	A Based on	WO 9716178 A
JP 11514629	W Based on	WO 9716178 A
EP 857064	B1 Based on	WO 9716178 A
DE 59609926	G Based on	WO 9716178 A

PRIORITY APPLN. INFO: DE 1995-19541128 19951027

INT. PATENT CLASSIF.:
MAIN: A61K031-195
IPC RECLASSIF.: A61K0031-00 [I,A]; A61K0031-00 [I,C]; A61K0031-185 [I,C]; A61K0031-195 [I,A]; A61K0031-197 [I,A]; A61K0031-198 [I,A]; A61K0047-02 [I,A]; A61K0047-02 [I,C]; A61K0047-04 [I,A]; A61K0009-20 [I,A]; A61K0009-20 [I,C]; A61P0005-00 [I,A]; A61P0005-00 [I,C]; A61P0005-14 [I,A]

BASIC ABSTRACT:

DE 19541128 A1 UPAB: 20060113 Stable thyroid hormone (I)-containing compositions comprise sodium thiosulphate (II) as the stabilising component. The weight ratio of (I):(II) is 1:0.1-1:50.

USE - The compositions are useful for treating various thyroid diseases, particularly in thyroid over- and under-production, iodine deficiency and related secondary diseases, and also for prophylactic substitution, optionally in combination with other agents e.g. iodine salts.

ADVANTAGE - The compositions containing (II) are more stable and have a longer shelf-life and can be kept for at least 3 years without any special protection (also in high temperature and humid climatic regions) with (I) hardly losing its full activity. The compositions can be easily prepared using a cheap and an environmental friendly process. MANUAL CODE: CPI: B04-J04; B05-A01B; B05-C05; B14-N11

Member(0002)

ABEQ WO 1997016178 A1 UPAB 20060113

Stable thyroid hormone (I)-containing compositions comprise sodium thiosulphate (II) as the stabilising component. The weight ratio of (I):(II) is 1:0.1-1:50.

USE - The compositions are useful for treating various thyroid diseases, particularly in thyroid over- and under-production, iodine deficiency and related secondary diseases, and also for prophylactic substitution, optionally in combination with other agents e.g. iodine salts.

ADVANTAGE - The compositions containing (II) are more stable and have a longer shelf-life and can be kept for at least 3 years without any special protection (also in high temperature and humid climatic regions) with (I) hardly losing its full activity. The compositions can be easily prepared using a cheap and an environmental friendly process.

ABDT DE19541128

Stable thyroid hormone (I) -containing compositions comprise sodium thiosulphate (II) as the stabilising component. The weight ratio of (I):(II) is 1:0.1-1:50.

USE

The compositions are useful for treating various thyroid diseases, particularly in thyroid over- and under-production, iodine deficiency and related secondary diseases, and also for prophylactic substitution. The compositions are used optionally in combination with other agents e.g. iodine salts.

Dosage of (I) is 25-300 μg per day for chronic therapy, and up to 1 mg for diagnostic purposes.

ADVANTAGE

The compositions containing (II) are more stable, have a longer shelf-life and can be kept for at least 3 years without any special protection (also in high temperature and humid climatic regions) and with (I) hardly losing its full activity.

The compositions can be easily prepared using a cheap and an environmental friendly process.

PREPARATION

The composition is prepared by dissolving (II) in water optionally together with the alkali component, and adding this to the mixture containing (I).

EXAMPLE
A composition comprising (in g): sodium levothyroxine (0.60), pregelatinised starch (225.00), maize starch (327.00), microcrystalline cellulose (334.63), (II) (3.00), sodium carbonate (0.77), hydrated castor oil (4.50), highly dispersed SiO2 (4.50), was prepared by dissolving the (II) and sodium carbonate in water and suspending the levothyroxine in the solution. A mixture of the microcrystalline cellulose and the suspension was granulated and the rest of the components added and mixed. The mixture was suitable for filling in hard gelatine capsules or pressing into tablets of desired active agent content.
A tablet containing 50 µg sodium levothyroxine and 500 µg sodium thiosulphate per 150 mg was packed in a blister pack and stability compared with a similar tablet containing no sodium thiosulphate. After 12 months at 30 °C/70% relative humidity, the tablet with thiosulphate showed 0.7% decomposition whilst the tablet without thiosulphate showed 12.8% decomposition. (MHG)
PREFERRED COMPOSITION
The composition further comprises an alkali component such that the aqueous solution has a pH 5.5-9. The alkali component is preferably sodium carbonate.
(I) is levothyroxine, liothyronine or diiodotyrosine.
The composition comprises at least two thyroid hormones and an additional active agent.

L86 ANSWER 30 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-536605 [50] WPIX
DOC. NO. CPI: C1997-171647 [50]
DOC. NO. NON-CPI: N1997-446669 [50]
TITLE: Controlled release hormone microsphere injection for treating obesity
DERWENT CLASS: A23; A25; A96; B01; P33
INVENTOR: CHENG L; ZHANG W; ZHENG Z
PATENT ASSIGNEE: (CHEN-N) CHENGDU INST ORGANIC CHEM CHINESE ACAD
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
CN 1127634	A	19960731	(199750)*	ZH		A61K009-56

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CN 1127634	A	CN 1995-111307	19950406

PRIORITY APPLN. INFO: CN 1995-111307 19950406
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61K0009-16 [I,A]; A61K0009-16 [I,C]
BASIC ABSTRACT:
CN 1127634 A UPAB: 20050519 Controlled release hormone microsphere injection comprises two components of aseptic powder containing polylactic acid, polyhydroxyl acetic acid, polylactic acid-polyethylene glycol, polyhydroxyacetic acid-polyethylene glycol, polylactic acid-polyhydroxyacetic acid, polyamino acid, **gelatin** and arabic gum and hormone such as oestradiol valerate, estriol, testosterone propionate, or thyroid powder, and 0.9% physiological saline containing silica oil and emulsifier.
USE - The injection is used for treating senile diseases caused by low sex hormone level. Its **thyroxine** preparation is used to treat obesity.

MANUAL CODE: CPI: A12-V01; B01-A02; B01-C05; B04-B01C3; B04-B04G; B04-C01; B04-C02D; B04-C03C; B04-C03D; B04-N02; B12-A03; B12-M10A; B14-E12; B14-P02

ALE Controlled release hormone microsphere injection comprises two components of aseptic powder containing polylactic acid, polyhydroxyl acetic acid, polylactic acid-polyethylene glycol, polyhydroxyacetic acid-polyethylene glycol, polylactic acid-polyhydroxyacetic acid, polyamino acid, **gelatin** and arabic gum and hormone such as oestradiol valerate, estriol, testosterone propionate, or thyroid powder, and 0.9% physiological saline containing silica oil and emulsifier.

USE USE - The injection is used for treating senile diseases caused by low sex hormone level. Its **thyroxine** preparation is used to treat obesity.

ABDT CN1127634
Controlled release hormone microsphere injection comprises two components of aseptic powder containing polylactic acid, polyhydroxyl acetic acid, polylactic acid-polyethylene glycol, polyhydroxyacetic acid-polyethylene glycol, polylactic acid-polyhydroxyacetic acid, polyamino acid, gelatin and arabic gum and hormone such as oestradiol valerate, estriol, testosterone propionate, or thyroid powder, and 0.9% physiological saline containing silica oil and emulsifier.
USE
The injection is used for treating senile diseases caused by low sex hormone level. Its thyroxine preparation is used to treat obesity.
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 31 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-527238 [49] WPIX
DOC. NO. CPI: C1997-167809 [49]
DOC. NO. NON-CPI: N1997-439259 [49]
TITLE: Injection of delayed hormone microcapsule
DERWENT CLASS: A96; B01; P33
INVENTOR: CHENG L; XUE Q; ZHANG W
PATENT ASSIGNEE: (CHEN-N) CHENGDU INST ORGANIC CHEM CHINESE ACAD
COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
CN 1126589	A	19960717	(199749)*	ZH		A61K009-66

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
CN 1126589	A	CN 1995-111394	19950609

PRIORITY APPLN. INFO: CN 1995-111394 19950609
INT. PATENT CLASSIF.:
IPC RECLASSIF.: A61J0003-00 [I,A]; A61J0003-00 [I,C]; A61K0009-52 [I,C]; A61K0009-66 [I,A]

BASIC ABSTRACT:
CN 1126589 A UPAB: 20050519 Injection of delayed hormone microcapsule comprises microcapsule bacteria-free powder of polylactate, polyhydroxyacetic acid, polyglycol, polyamino acid, **gelatin** or gum arabic containing valeric estradiol, estriol, propinate testosterone, **thyroxine** powder or other hormone.
USE - The injection is used for treating senile diseases caused by reduced hormone levels and obesity. MANUAL CODE: CPI: A12-V01; A12-W05; B01-A02; B01-C05; B04-C01;

B04-C03C; B04-C03D; B04-J01; B14-J01A4

ALE Injection of delayed hormone microcapsule comprises microcapsule bacteria-free powder of polylactate, polyhydroxyacetic acid, polyglycol, polyamino acid, **gelatin** or gum arabic containing valeric estradiol, estriol, propinate testosterone, **thyroxine** powder or other hormone.

ABDT CN1126589

Injection of delayed hormone microcapsule comprises microcapsule bacteria-free powder of polylactate, polyhydroxyacetic acid, polyglycol, polyamino acid, gelatin or gum arabic containing valeric estradiol, estriol, propinate testosterone, thyroxine powder or other hormone.

USE

The injection is used for treating senile diseases caused by reduced hormone levels and obesity.

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 32 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN

ACCESSION NUMBER: 1993-100651 [12] WPIX

CROSS REFERENCE: 1995-381884; 1997-086657

DOC. NO. CPI: C1993-044367 [21]

TITLE: Wound treatment formulations used for promoting healing - comprising a cellular growth stimulating cpd. in a cellular nutrient medium

DERWENT CLASS: A96; B04; P34

INVENTOR: LINDENBAUM E

PATENT ASSIGNEE: (LIFE-N) LIFE MEDICAL SCI INC; (TECR-C) TECHNION RES & DEV FOUND LTD

COUNTRY COUNT: 35

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 9304691	A1	19930318	(199312)*	EN	47[7]	A61K037-02
AU 9225879	A	19930405	(199330)	EN		A61K037-02
FI 9400932	A	19940228	(199418)	FI		A61K000-00
NO 9400406	A	19940328	(199422)	NO		A61K037-02
BR 9206433	A	19940927	(199440)	PT		A61K037-02
JP 06510453	W	19941124	(199506)	JA	14	A61L015-44
HU 67319	T	19950328	(199518)	HU		A61K037-02
EP 650366	A1	19950503	(199522)	EN		A61K037-02
AU 670413	B	19960718	(199639)	EN		A61K037-26
EP 650366	B1	19991124	(199954)	EN		A61K038-00
DE 69230344	E	19991230	(200007)	DE		A61K038-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9304691 A1		WO 1992-US7341	19920828
AU 9225879 A		AU 1992-25879	19920828
AU 670413 B		AU 1992-25879	19920828
BR 9206433 A		BR 1992-6433	19920828
DE 69230344 E		DE 1992-69230344	19920828
EP 650366 A1		EP 1992-919722	19920828
EP 650366 B1		EP 1992-919722	19920828
DE 69230344 E		EP 1992-919722	19920828
FI 9400932 A		WO 1992-US7341	19920828
NO 9400406 A		WO 1992-US7341	19920828
BR 9206433 A		WO 1992-US7341	19920828

JP 06510453 W	WO 1992-US7341 19920828
HU 67319 T	WO 1992-US7341 19920828
EP 650366 A1	WO 1992-US7341 19920828
EP 650366 B1	WO 1992-US7341 19920828
DE 69230344 E	WO 1992-US7341 19920828
JP 06510453 W	JP 1993-505336 19920828
HU 67319 T	HU 1994-593 19920828
NO 9400406 A	NO 1994-406 19940208
FI 9400932 A	FI 1994-932 19940228

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 670413 B	Previous Publ	AU 9225879 A
DE 69230344 E	Based on	EP 650366 A
AU 9225879 A	Based on	WO 9304691 A
BR 9206433 A	Based on	WO 9304691 A
JP 06510453 W	Based on	WO 9304691 A
HU 67319 T	Based on	WO 9304691 A
EP 650366 A1	Based on	WO 9304691 A
AU 670413 B	Based on	WO 9304691 A
EP 650366 B1	Based on	WO 9304691 A
DE 69230344 E	Based on	WO 9304691 A

PRIORITY APPLN. INFO: US 1991-752849 19910830
INT. PATENT CLASSIF.:
MAIN: A61K038-00; A61L015-44
IPC RECLASSIF.: A61K [I,S]; A61K0031-045 [I,C]; A61K0031-05 [I,A]; A61K0031-185 [I,C]; A61K0031-198 [I,A]; A61K0031-545 [I,A]; A61K0031-545 [I,C]; A61K0031-57 [I,A]; A61K0031-57 [I,C]; A61K0031-65 [I,A]; A61K0031-65 [I,C]
SECONDARY: A61K037-24; A61K037-26 [I,A]; A61K0038-18 [I,C]; A61K0038-22 [I,A]; A61K0038-22 [I,C]; A61K0038-27 [I,A]; A61K0038-27 [I,C]; A61K0038-28 [I,A]; A61K0038-28 [I,C]; A61K0038-40 [I,A]; A61K0038-40 [I,C]; A61K0047-30 [I,A]; A61K0047-30 [I,C]; A61K0009-06 [I,A]; A61K0009-06 [I,C]; A61K0009-08 [I,A]; A61K0009-08 [I,C]; A61L0015-16 [I,C]; A61L0015-44 [I,A]; A61L0026-00 [I,A]; A61L0026-00 [I,C]; A61P0017-00 [I,A]; A61P0017-00 [I,C]; A61P0043-00 [I,A]; A61P0043-00 [I,C]
; A61K0038-18

BASIC ABSTRACT:

WO 1993004691 A1 UPAB: 20060107 Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concentration of at least ca. 0.05 mg/ml) in a cellular nutrient medium. Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free. Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feee), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addition of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), especially MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amount ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (especially

hydroxymethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, especially a celaphosporin or tetracycline. The formulation is delivered as a solution, a gel (especially derived from **gelatin** or agarose) or a cream.

USE/ADVANTAGE - The compsn. is used for promoting wound healing in skin and related tissues. It is useful for treating punctures, incisions, excisions, lacerations, abrasions and burns, including large burn areas. The compsn. accelerates wound healing and also prolongs the viability in skin and other tissu

MANUAL CODE: CPI: A12-V01; B04-B04L; B12-A07

Member(0006)

ABEQ JP 06510453 W UPAB 20060107

Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concn. of at least ca. 0.05 mg/ml) in a cellular nutrient medium.

Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free.

Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feed), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addn. of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), esp. MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amt. ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (esp. hydroxymethacrylate, polyvinylpyrrolidine, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, esp. a cephalosporin or tetracycline. The formulation is delivered as a soln., a gel (esp. derived from **gelatin** or agarose) or a cream.

USE/ADVANTAGE - The compsn. is used for promoting wound healing in skin and related tissues. It is useful for treating punctures, incisions, excisions, lacerations, abrasions and burns, including large burn areas. The compsn. accelerates wound healing and also prolongs the viability in skin and other tissue.

Member(0010)

ABEQ EP 650366 B1 UPAB 20060107

Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concn. of at least ca. 0.05 mg/ml) in a cellular nutrient medium.

Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free.

Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feee), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addn. of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), esp. MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or

mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amt. ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (esp. hydroxymethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, esp. a celaphosporin or tetracycline. The formulation is delivered as a soln., a gel (esp. derived from **gelatin** or agarose) or a cream.

USE/ADVANTAGE - The compsn. is used for promoting wound healing in skin and related tissues. It is useful for treating punctures, incisions, excisions, lacerations, abrasions and burns, including large burn areas. The compsn. accelerates wound healing and also prolongs the viability in skin and other tissu

ALE Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concn. of at least ca. 0.05 mg/ml) in a cellular nutrient medium. Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free.
Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feee), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addn. of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification. Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), esp. MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amt. ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (esp. hydroxymethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, esp. a celaphosporin or tetracycline. The formulation is delivered as a soln., a gel (esp. derived from **gelatin** or agarose) or a cream.

Member(0.006)

ABEQ JP 06510453 W UPAB 20060107
Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concn. of at least ca. 0.05 mg/ml) in a cellular nutrient medium. Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free.
Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feed), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addn. of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), esp. MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amt. ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (esp. hydroxymethacrylate,

polyvinylpyrrolidine, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, esp. a cephalosporin or tetracycline. The formulation is delivered as a soln., a gel (esp. derived from **gelatin** or agarose) or a cream.

USE/ADVANTAGE - The compsn. is used for promoting wound healing in skin and related tissues. It is useful for treating punctures, incisions, excisions, lacerations, abrasions and burns, including large burn areas. The compsn. accelerates wound healing and also prolongs the viability in skin and other tissue.

Member(0010)
ABEQ EP 650366 B1 UPAB 20060107
Wound-treatment formulation comprises a cellular growth stimulating cpd. (at a concn. of at least ca. 0.05 mg/ml) in a cellular nutrient medium.
Method for treating wounds comprises applying a formulation as above, where the cellular nutrient medium is serum free.
Pref. the nutrient medium is serum free and is selected from ADC-1, LPM (albumin-feee), F10, F12, DCCM1, DCCM2, BGJ medium (Fitton-Jackson modification), Basal Medium Eagle (with the addn. of Earle's salt base), Dulbecco's modified Eagle medium (without serum), Glasgow modification Eagle Medium, Leibovitz L-15 Medium, McCoy's 5A Medium, MDCB 153, Medium M199 (M199E with Earle's salt base or M199H with Hank's salt base) or Minimum Essential Medium Eagle (MEM-E with Earle's salt base), MEM-H with Hank's salt base, or with non-essential amino acids), esp. MDCB 153. The cellular growth stimulating cpd. is a growth hormone, **thyroxin**, triidothyronine, insulin, epithelial growth factor, transforming growth factor, platelet derived growth factor, insulin-like growth factor, or mixts. of these. The cpd. is e.g. human growth hormone in the range of 0.5-50 microg/ml, or insulin in an amt. ranging from 5 mg/ml to 100 microg/ml. The formulation also comprises hydrocortisone (0.1-50 micro-mol.), a delivery polymer (esp. hydroxymethacrylate, polyvinylpyrrolidone, polyethylene glycol, **gelatin**, agarose, collagen and/or a hydrophilic cellulose polymer) and an antimicrobial agent, esp. a celaphosporin or tetracycline. The formulation is delivered as a soln., a gel (esp. derived from **gelatin** or agarose) or a cream.

USE/ADVANTAGE - The compsn. is used for promoting wound healing in skin and related tissues. It is useful for treating punctures, incisions, excisions, lacerations, abrasions and burns, including large burn areas. The compsn. accelerates wound healing and also prolongs the viability in skin and other tissu
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 33 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-026804 [04] WPIX
DOC. NO. CPI: C1992-011501 [21]
TITLE: Pharmaceutical compsn. containing vegetable dye - ensures against photodecomposition in processing and after, may also improve drug solubility and release
DERWENT CLASS: A96; B03; B05; B07
INVENTOR: BALAZS R; CSOERGO M; CSOERGOE M; CSORGO M; JUDIT-NEE-JUHASZ T E; KATALIN-NEE-NAGY W; MANDI A; MANDI A M J; MARCISZ J; NAGY K; NAGY M; NAGY M N K; TAJTHY E; TAJTHY E J; TAJTHY T; WAGNER I; WAGNER K
PATENT ASSIGNEE: (EGYE-C) EGIS GYOGYSZERGYAR; (EGYE-C) EGYT GYOGYSZERGYAR
COUNTRY COUNT: 19

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
GB 2246072	A	19920122	(199204)*	EN		
DE 4124081	A	19920123	(199205)	DE		
NL 9101268	A	19920217	(199211)	NL	18[4]	
SE 9102160	A	19920121	(199213)	SV		
FR 2664814	A	19920124	(199214)	FR	20	
CA 2047482	A	19920121	(199215)	EN		
DK 9101375	A	19920121	(199216)	DA		
FI 9103493	A	19920121	(199217)	FI		
HU 59592	T	19920629	(199231)	HU		A61K009-48
CS 9102222	A2	19920219	(199238)	CS		A61K047-22
JP 04253924	A	19920909	(199243)	JA	9	A61K047-46
ZA 9105677	A	19930331	(199319)	EN	23	A61K000-00
CH 681960	A5	19930630	(199330)	DE		A61K047-00
TW 203012	A	19930401	(199333)	ZH		A61K009-48
ES 2039177	A1	19930901	(199340)	ES		A61K009-48
ES 2039177	B1	19940316	(199415)	ES		A61K009-48
GB 2246072	B	19940615	(199421)	EN	[0]	A61K009-48
BE 1006829	A3	19950103	(199506)	FR	23[0]	A61K000-00
IT 1250681	B	19950421	(199544)	IT		A61K000-00
CZ 280064	B6	19951018	(199549)	CS		A61K047-22
RU 2053764	C1	19960210	(199645)#	RU	7[0]	A61K009-00

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
GB 2246072 A		GB 1991-15693	19910719
FR 2664814 A		FR 1990-9183	19900709
HU 59592 T		HU 1990-4564	19900720
CH 681960 A5		CH 1991-2125	19910717
CS 9102222 A2		CS 1991-2222	19910717
CZ 280064 B6		CS 1991-2222	19910717
BE 1006829 A3		BE 1991-683	19910719
DE 4124081 A		DE 1991-4124081	19910719
ES 2039177 A1		ES 1991-1701	19910719
ES 2039177 B1		ES 1991-1701	19910719
GB 2246072 B		GB 1991-15693	19910719
IT 1250681 B		IT 1991-MI2002	19910719
JP 04253924 A		JP 1991-203542	19910719
NL 9101268 A		NL 1991-1268	19910719
RU 2053764 C1		SU 1991-5001143	19910719
TW 203012 A		TW 1991-105605	19910719
ZA 9105677 A		ZA 1991-5677	19910719

FILING DETAILS:

PATENT NO	KIND	PATENT NO
CZ 280064 B6	Previous Publ	CS 9102222 A

PRIORITY APPLN. INFO: HU 1990-4564 19900720
SU 1991-5001143 19910719
INT. PATENT CLASSIF.:
MAIN: A61K009-48
IPC RECLASSIF.: A61K0031-045 [I,C]; A61K0031-047 [I,A]; A61K0031-07 [I,A] ; A61K0031-13 [I,A]; A61K0031-13 [I,C]; A61K0031-135 [I,A]; A61K0031-135 [I,C]; A61K0031-165 [I,A]; A61K0031-165 [I,C]; A61K0031-185 [I,C]; A61K0031-19 [I,A]

; A61K0031-195 [I,A]; A61K0031-21 [I,A]; A61K0031-21 [I,C]; A61K0031-345 [I,A]; A61K0031-345 [I,C]; A61K0031-40 [I,A]; A61K0031-40 [I,C]; A61K0031-415 [I,A]; A61K0031-415 [I,C]; A61K0031-44 [I,A]; A61K0031-44 [I,C]; A61K0031-455 [I,A]; A61K0031-455 [I,C]; A61K0031-46 [I,A]; A61K0031-46 [I,C]; A61K0031-47 [I,A]; A61K0031-47 [I,C]; A61K0031-475 [I,A]; A61K0031-475 [I,C]; A61K0031-48 [I,A]; A61K0031-48 [I,C]; A61K0031-485 [I,A]; A61K0031-485 [I,C]; A61K0031-495 [I,A]; A61K0031-495 [I,C]; A61K0031-519 [I,C]; A61K0031-52 [I,A]; A61K0031-565 [I,A]; A61K0031-565 [I,C]; A61K0031-57 [I,A]; A61K0031-57 [I,C]; A61K0031-59 [I,A]; A61K0031-59 [I,C]; A61K0031-63 [I,A]; A61K0031-63 [I,C]; A61K0038-22 [I,A]; A61K0038-22 [I,C]

SECONDARY: A61K047-22; A61K0047-46 [I,A]; A61K0047-46 [I,C]; A61K0009-00 [I,A]; A61K0009-00 [I,C]; A61K0009-28 [I,A]; A61K0009-28 [I,C]; A61K0009-30 [I,C]; A61K0009-40 [I,A]; A61K0009-48 [I,A]; A61K0009-48 [I,C]

BASIC ABSTRACT:

GB 2246072 A UPAB: 20060106 A solid pharmaceutical compsn. comprises: (a) a light-sensitive and opt. hardly water soluble active ingredient; (b) a vegetable dye; and (c) conventional carriers and/or auxiliary agents. Pref. active ingredients vitamins D, vitamin A; imidazolines and piperazines etc.. The dye is pref. chlorophyll (either lipophilic or hydrophilic).

USE/ADVANTAGE - Decomposition prods. of light-sensitive materials may include inactive or harmful cpds., for which regulations become more severe. The compsn. provides protection of the active materia MANUAL CODE: CPI: A12-V01; B04-B01B; B04-B01C1; B04-N02; B05-B01P; B06-D18; B07-D04C; B07-D04D; B12-M10A; B12-M11C

Member(0005)

ABEQ FR 2664814 A UPAB 20060106

A solid pharmaceutical compsn. comprises (a) a light-sensitive and opt. hardly water soluble active ingredient; (b) a vegetable dye; and (c) conventional carriers and/or auxiliary agents. Pref. active ingredients are vitamins D, vitamin A; imidazolines and iperazines etc., The dye is pref. chlorophyll (either lipophilic or hydrophilic).

USE/ADVANTAGE - Decomposition prods. of light-sensitive materials may include inactive or harmful cpds., for which regulations become more severe. The compsn. provides protection of the active material throughout formulation operations and for the finished prod., without extra steps or equipment, in an easily feasible process. The vegetable dye may also improve the solubility of active ingredient, e.g. nifedipine, in the carrier, improving release characteristics. The dyestuff is opt. also incorporated in the wall of soft **gelatin** capsules. Formulations also include tablets, deragees, or hard **gelatin** capsules.

Member(0012)

ABEQ ZA 9105677 A UPAB 20060106

The solid pharmaceutical compositions, pref. soft **gelatin** capsules, comprising a light-sensitive active ingredient opt. being hardly soluble in water, pref. nifedipine (4-(2'-nitrophenyl)--2,6-dimethyl-3,5-dimethoxycarbonyl-1,4- dihydropyridine), together with conventional carriers and/or auxiliary agents, wherein the compsn. incorporates a vegetable dye.

USE/ADVANTAGE - The incorporation of a vegetable dye into the capsule wall ensures a reliable light protection during the mfg. and filling operations and improves the solubility of nifedipine in certain carriers.

Member(0018)
ABEQ BE 1006829 A3 UPAB 20060106
A solid pharmaceutical compsn. comprises (a) a light-sensitive opt. hardly water soluble active ingredient; (b) a vegetable dye; and (c) conventional carriers and/or auxiliary agents.
Pref. active ingredients are vitamin D, vitamin A, imidazolines and piperazines etc.. The dye is pref. chlorophyll (either lipophilic or hydrophilic).
USE/ADVANTAGE - Decompsn. prods. of light-sensitive materials may include inactive or harmful cpds. for which regulations become more severe. The compsn. provides protection of the active material throughout formulation operations and for the finished prod., without extra steps or equipment, in an easily feasible process. The vegetable dye may also improve the solubility of the active ingredient, e.g. nifedipine in the carrier, improving release characteristics.

Member(0021)
ABEQ RU 2053764 C1 UPAB 20060106
Pharmaceutical prepns. contg. light-sensitive and low-solubility biologically-active substits., particularly 'nifedipin' (sic), a widely-used calcium channel blocker, can be obtd. in the form of capsules comprising a soft **gelatine** shell and a light-protecting fill material. The latter consists of the following components (wt. %): 'nifedipin' dihydropyridine deriv. (2-5); hydrophilic or lipophilic chlorophyll as vegetable pigment (0.1-10.0); vegetable oil or other suitable solvent (90-96).
USE - Prepns. are used in pharmaceutical mfr.
ADVANTAGE - The calcium channel-blocking dihydropyridine deriv. is protected from decompn. by light.
ABDT RU2053764
Pharmaceutical prepns. contg. light-sensitive and low-solubility biologically-active substits., particularly nifedipine, a widely-used calcium channel blocker, can be obtd. in the form of capsules comprising a soft gelatine shell and a light-protecting fill material. The latter consists of the following components (wt. %):
nifedipine dihydropyridine deriv. (2-5);
hydrophilic or lipophilic chlorophyll as vegetable pigment (0.1-10.0);
vegetable oil or other suitable solvent (90-96).
USE
Prepns. are used in pharmaceutical mfr.
ADVANTAGE
The calcium channel-blocking dihydropyridine deriv. is protected from decomposition by light.
EXAMPLE
First nifedipine (3.00 wt. %) was dissolved in polyethylene-oxide sorbitan monooleate (22.85), heated to 70 °C. When lecithin (57.00) and lipophilic chlorophyll (2.50) had been mixed in, the soln. was cooled to room temp. and lemon oil (14.65) was added to it before filtration. (AB)
IT UPIT 20060106
102039-CMP; 102064-CMP; 102107-CMP 102107-USE; 102110-CMP 102110-USE; 102123-CMP; 104702-CMP; 105509-CMP 105509-USE; 108000-CMP 108000-USE; **108879-CMP 108879-USE**; 109403-CMP 109403-USE; 109488-CMP 109488-USE; 129776-USE; 129913-USE; 130130-USE; 130313-USE; 131095-USE; 132054-CMP; 132199-USE; 133373-USE; 133420-USE; 134726-USE; 134872-USE; 139868-USE; 140561-CMP; 140942-CMP 140942-USE; 143149-CMP; 148651-USE; 148654-CMP 148654-USE; 150711-CMP 150711-USE; 1884-USE; 192312-USE; 2623-USE; 44063-CMP 44063-USE; 44586-CMP; 589-USE; 60080-CMP 60080-USE; 6103-CMP 6103-USE; 61832-USE; 6679-USE; 67535-CMP 67535-USE; 6754-CMP; 70204-CMP; 7127-USE; 72610-CMP; 7903-CMP 7903-USE; 88150-CMP 88150-USE;

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      88752-CMP 88752-USE; 90794-CMP; 90795-CMP; 90868-USE; 91432-USE;
      91462-CMP; 91464-CMP 91464-USE; 93718-CMP; 94397-USE; 96686-CMP 96686-USE;
      98315-CMP 98315-USE
CMC   UPB   20060106
      DRN: 0007-U 0018-U 0026-U 0050-U 0053-U 0066-U 0078-U 0096-U
           0127-U 0171-U 0180-U 0267-U 0276-U 0282-U 0283-U 0540-U 0590-U 0958-U
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      DCR: 102107-U 102110-U 105509-U 108000-U 108879-U 109403-U
           109488-U 129776-U 129913-U 130130-U 130313-U 131095-U 132199-U
           133373-U 133420-U 134726-U 134872-U 139868-U 140942-U 148651-U
           148654-U 150711-U 1884-U 192312-U 2623-U 44063-U 589-U 60080-U 6103-U
           61832-U 6679-U 67535-U 7127-U 7903-U 88150-U 88752-U 90868-U 91432-U
           91464-U 94397-U 96686-U 98315-U
      M1 *19*   M421 M423 M431 M782 Q312 R031 V000 V131 V470 V624 V795  M903
      M2 *01*   F012 F013 F014 F015 F016 F432 G010 G011 G012 G100 H103 H181 H3
                H341 H581 J0 J012 J2 J212 M1 M113 M210 M211 M212 M213 M232 M240
                M272 M273 M281 M282 M311 M312 M320 M321 M332 M342 M373 M383 M391
                M413 M431 M510 M521 M531 M540 M782  M903 M904
                DCN: R03027-M R06632-M R07653-M R07654-M R08449-M
                DCR: 102039-M 102064-M 44586-M 6754-M 72610-M
      M2 *02*   G031 G036 G039 G060 G563 G640 H4 H401 H461 H7 H720 H721 H725 H8
                M1 M126 M134 M210 M211 M220 M223 M232 M240 M282 M311 M312 M321
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                V340  M903 M904 M910
                RIN: 01391
                DCN: R00007-M
                DCR: 6103-M
      M2 *03*   G036 G038 G562 H4 H401 H481 H7 H725 H8 M210 M211 M240 M283 M316
                M321 M333 M342 M373 M391 M415 M431 M510 M520 M530 M541 M782 Q312
                R031 V0 V310  M903 M904 M910
                DCN: R00282-M
                DCR: 105509-M
      M2 *04*   D013 D016 D019 D030 E320 E530 G010 G100 H1 H181 H2 H201 H4 H401
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                RIN: 02319
                DCN: R07361-M
                DCR: 143149-M
      M2 *05*   D012 D013 D940 G013 G100 H1 H101 H103 H122 H141 J0 J013 J1 J172
                J3 J331 L9 L910 M210 M211 M273 M281 M311 M313 M321 M332 M342
                M343 M349 M373 M381 M391 M412 M431 M511 M520 M531 M540 M782 Q312
                R031  M903 M904 M910
                DCN: R00180-M
                DCR: 60080-M
      M2 *06*   F011 F012 F014 F015 F019 F111 F523 H2 H211 H3 H321 J5 J522 K0 K6
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                R031  M903 M904 M910
                DCN: R00267-M
                DCR: 102107-M
      M2 *08*   D011 D021 D029 E550 H1 H181 H2 H201 H4 H402 H441 H461 H8 M210
                M211 M273 M281 M320 M412 M431 M511 M520 M530 M540 M640 M782 Q312
                R031 V0 V441  M903 M904 M910
                DCN: R07434-M
                DCR: 148654-M
      M2 *09*   D011 D023 D631 G015 G100 H5 H543 H8 M1 M123 M132 M210 M211 M272
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                R031 V0 V440  M903 M904 M910
                DCN: R04935-M
                DCR: 150711-M
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M2 *10* G015 G100 H1 H100 H181 H4 H402 H442 H8 M280 M312 M321 M332 M342 M373 M391 M414 M431 M510 M520 M531 M540 M782 Q312 R031 M903 M904 M910
DCN: R00053-M
DCR: 7903-M

M2 *11* G015 G100 H1 H102 H181 H4 H403 H442 H481 H8 M210 M213 M232 M273 M281 M312 M321 M332 M343 M373 M391 M414 M431 M510 M520 M531 M540 M782 Q312 R031 M903 M904 M910
DCN: R01723-M
DCR: 98315-M

M2 *12* C316 F012 F541 G013 G100 H1 H100 H141 K0 K3 K353 L9 L922 M1 M123 M147 M280 M320 M413 M431 M510 M521 M531 M540 M782 Q312 R031 M903 M904 M910
DCN: R00283-M
DCR: 108000-M

M2 *13* D011 E130 H2 H211 K0 L4 L432 M280 M320 M412 M431 M511 M520 M530 M540 M782 Q312 R031 M903 M904 M910
DCN: R01203-M
DCR: 44063-M

M2 *14* D011 D022 E800 F011 F014 F553 H1 H183 H2 H203 H6 H685 M210 M211 M273 M281 M311 M313 M321 M332 M342 M344 M353 M383 M391 M412 M431 M511 M521 M530 M540 M782 Q312 R031 M903 M904 M910
DCN: R00983-M
DCR: 109403-M

M2 *15* D011 D014 D670 G010 G100 H1 H181 H2 H201 J0 J012 J2 J211 J221 M1 M123 M136 M210 M211 M272 M273 M281 M320 M412 M431 M511 M520 M531 M540 M640 M782 Q312 R031 V0 V411 M903 M904 M910
DCN: R11463-M
DCR: 140942-M

M2 *16* F012 F431 G010 G100 H1 H103 H121 H181 L9 L943 M210 M211 M273 M282 M311 M312 M321 M332 M373 M383 M391 M413 M431 M510 M521 M531 M540 M782 Q312 R031 M903 M904 M910
DCN: R00590-M
DCR: 109488-M

M2 *17* D011 D022 D621 H1 H102 H103 H121 H181 H6 H602 H641 M210 M212 M273 M282 M315 M321 M331 M342 M383 M391 M412 M431 M511 M520 M530 M540 M782 Q312 R031 M903 M904 M910
DCN: R00078-M
DCR: 67535-M

M2 *18* K0 K7 K710 K799 M280 M313 M321 M332 M343 M383 M391 M416 M431 M620 M782 Q312 R031 M903 M904 M910
DCN: R00096-M
DCR: 102110-M

M2 *20* A212 A960 C710 D011 D013 D019 D023 E350 H7 H715 H721 H722 J0 J012 J2 J251 J271 J411 J5 J561 M210 M211 M212 M226 M232 M240 M272 M282 M283 M312 M321 M332 M342 M372 M391 M411 M431 M511 M520 M530 M540 M782 Q312 R031 M903 M904
RIN: 06561
DCN: R09012-M R10075-M R10092-M
DCR: 132054-M 90794-M 90795-M

M2 *21* G013 G100 J0 J011 J3 J331 K0 K6 K640 M210 M211 M213 M232 M273 M282 M311 M321 M342 M373 M391 M414 M431 M510 M520 M531 M540 M782 Q312 R031 M903 M904
DCN: R08235-M
DCR: 104702-M

M2 *22* G023 G031 G033 G380 H5 H543 H561 H8 J0 J011 J3 J361 J5 J561 M210 M211 M262 M272 M281 M283 M320 M414 M431 M510 M520 M531 M540 M782 Q312 R031 V0 V470 M903 M904
DCN: R10166-M
DCR: 91462-M

M2 *23* G010 G012 G100 J0 J011 J1 J171 J5 J581 M1 M121 M131 M150 M280 M312 M321 M331 M340 M342 M372 M391 M414 M431 M510 M520 M532 M540 M782 Q312 R031 M903 M904
DCN: R03908-M
DCR: 70204-M

M2 *24* H4 H402 H482 H8 J0 J012 J1 J172 M280 M312 M321 M332 M344 M349 M381 M391 M416 M431 M620 M771 M782 Q312 R031 M903 M904 M910
DCN: R07361-M
DCR: 143149-M

M2 *25* D011 D022 E800 H1 H103 H182 H2 H201 H6 H602 H641 M210 M211 M273 M282 M313 M321 M332 M342 M383 M391 M412 M431 M511 M520 M530 M540 M640 M782 Q312 R031 M903 M904 M910
DCN: R07808-M
DCR: 140561-M

M2 *26* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 M800 Q312 R031 M903 M904 M910
DCN: **R04769-M**
DCR: **108879-M**

M2 *27* D011 D931 F011 F014 F015 F521 H1 H181 H2 H201 H3 H321 H5 H592 H9 L9 L943 L999 M1 M126 M142 M210 M211 M273 M281 M320 M412 M431 M511 M521 M530 M540 M782 Q312 R031 M903 M904 M910
DCN: R01259-M
DCR: 88150-M

M2 *28* A111 A426 A940 A980 C106 C107 C108 C520 C730 C801 C802 C803 C807 M411 M431 M782 Q312 R031 M903 M904
DCN: R06406-M
DCR: 102123-M

M2 *29* G031 G036 G039 G060 G563 G640 H4 H401 H461 H7 H720 H725 H8 M1 M126 M134 M210 M211 M220 M222 M232 M240 M282 M311 M312 M321 M332 M341 M344 M415 M431 M510 M520 M530 M542 M782 Q312 R031 V0 V340 M903 M904 M910
RIN: 01391
DCN: R00276-M
DCR: 91464-M

M2 *30* F011 F014 F017 F433 G013 G019 G100 H1 H181 H2 H201 H4 H401 H421 H6 H601 H602 H642 H8 J5 J581 M1 M113 M280 M313 M321 M332 M342 M381 M391 M413 M431 M510 M521 M532 M540 M782 Q312 R031 M903 M904 M910
DCN: R00066-M
DCR: 96686-M

M2 *31* D013 D712 F011 F014 F432 F433 G013 G100 H1 H181 H2 H201 H211 H6 H601 H641 J5 J521 J581 L9 L921 M280 M313 M321 M332 M342 M381 M391 M412 M431 M511 M521 M531 M540 M782 Q312 R031 M903 M904
DCN: R03805-M
MCN: 9204-13501-M
DCR: 93718-M

M5 *07* M431 M782 Q312 R031 S001 S004 S030 S132 S133 S134 S142 S209 S217 S311 S316 S317 S511 S517 S521 S603 S620 T209 T230 T816 U016 U030 U520 M903 M904 M910
DCN: R01242-M
DCR: 88752-M

DRN 0007-U 0018-U 0026-U **0050-U** 0053-U 0066-U 0078-U 0096-U 0127-U 0171-U 0180-U 0267-U 0276-U 0282-U 0283-U 0540-U 0590-U 0958-U 0983-U 1203-U 1242-U 1259-U 1723-U

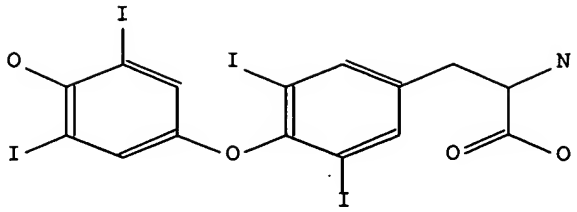
M2 *26* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 M800 Q312 R031 M903 M904 M910

DCN: **R04769-M**
DCR: **108879-M**

Member(0005)
ABEQ FR 2664814 A UPAB 20060106
A solid pharmaceutical compsn. comprises (a) a light-sensitive and opt. hardly water soluble active ingredient; (b) a vegetable dye; and (c) conventional carriers and/or auxiliary agents. Pref. active ingredients are vitamins D, vitamin A; imidazolines and iperazines etc., The dye is pref. chlorophyll (either lipophilic or hydrophilic).
USE/ADVANTAGE - Decomposition prods. of light-sensitive materials may include inactive or harmful cpds., for which regulations become more severe. The compsn. provides protection of the active material throughout formulation operations and for the finished prod., without extra steps or equipment, in an easily feasible process. The vegetable dye may also improve the solubility of active ingredient, e.g. nifedipine, in the carrier, improving release characteristics. The dyestuff is opt. also incorporated in the wall of soft **gelatin** capsules. Formulations also include tablets, deragees, or hard **gelatin** capsules.

Member(0012)
ABEQ ZA 9105677 A UPAB 20060106
The solid pharmaceutical compositions, pref. soft **gelatin** capsules, comprising a light-sensitive active ingredient opt. being hardly soluble in water, pref. nifedipine (4-(2'-nitrophenyl)--2,6-dimethyl-3,5-dimethoxycarbonyl-1,4- dihydropyridine), together with conventional carriers and/or auxiliary agents, wherein the compsn. incorporates a vegetable dye.
USE/ADVANTAGE - The incorporation of a vegetable dye into the capsule wall ensures a reliable light protection during the mfg. and filling operations and improves the solubility of nifedipine in certain carriers.

Member(0021)
ABEQ RU 2053764 C1 UPAB 20060106
Pharmaceutical prepns. contg. light-sensitive and low-solubility biologically-active substits., particularly 'nifedipin' (sic), a widely-used calcium channel blocker, can be obtd. in the form of capsules comprising a soft **gelatine** shell and a light-protecting fill material. The latter consists of the following components (wt. %): 'nifedipin' dihydropyridine deriv. (2-5); hydrophilic or lipophilic chlorophyll as vegetable pigment (0.1-10.0); vegetable oil or other suitable solvent (90-96).
USE - Prepns. are used in pharmaceutical mfr.
ADVANTAGE - The calcium channel-blocking dihydropyridine deriv. is protected from decompn. by light.
AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 34 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1987-095065 [14] WPIX
DOC. NO. CPI: C1987-039506 [21]
TITLE: Hard **gelatin** capsule containing chewable compsn. - comprises semi-solid ingredient, carrier and masticatory enhancing agent for buccal absorption or sublingual admin.
DERWENT CLASS: A25; A96; B07; P33
INVENTOR: JONES B E; KNIGHT P M; WALKER M A
PATENT ASSIGNEE: (ELIL-C) LILLY IND LTD; (SHIO-C) SHIONOGI EURO BV
COUNTRY COUNT: 24

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
EP 215635	A	19870325	(198714)*	EN	6	
AU 8662455	A	19870312	(198717)	EN		
DK 8604338	A	19870312	(198725)	DA		
JP 62116508	A	19870528	(198727)	JA		
PT 83327	A	19871020	(198746)	PT		
ZA 8606849	A	19870923	(198751)	EN		
HU 43951	T	19880128	(198810)	HU		
CN 86106150	A	19870318	(198823)	ZH		
US 4755389	A	19880705	(198829)	EN	3	A61K009-52
ES 2002302	A	19880801	(198926)	ES		
IL 79973	A	19900610	(199030)	EN		
CA 1273295	A	19900828	(199040)	EN		
EP 215635	B	19911113	(199146)	EN		A61K009-60
DE 3682467	G	19920227	(199210)	DE		
RU 2018305	C1	19940830	(199516)	RU	5[0]	A61K009-48
CN 1026463	C	19941109	(199544)	ZH		A61K009-48
KR 9402656	B1	19940328	(199602)	KO		A61K009-48
JP 08009535	B2	19960131	(199609)	JA	4[0]	A61K009-48
DK 174973	B	20040405	(200425)	DA		A61K009-66

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 215635 A		EP 1986-306968	19860910
CN 1026463 C		CN 1986-106150	19860908
JP 62116508 A		JP 1986-212527	19860909
JP 08009535 B2		JP 1986-212527	19860909
ZA 8606849 A		ZA 1986-6849	19860909
DK 174973 B		DK 1986-4338	19860910
ES 2002302 A		ES 1986-1759	19860910
KR 9402656 B1		KR 1986-7591	19860910

RU 2018305 C1 SU 1986-4028207 19860910
US 4755389 A US 1986-905905 19860910

FILING DETAILS:

PATENT NO	KIND	PATENT NO
DK 174973 B	Previous Publ	DK 8604338 A
JP 08009535 B2	Based on	JP 62116508 A

PRIORITY APPLN. INFO: GB 1985-22453 19850911
INT. PATENT CLASSIF.:
MAIN: A61K009-48
IPC RECLASSIF.: A61K0047-00 [I,A]; A61K0047-00 [I,C]; A61K0047-02 [I,A]; A61K0047-02 [I,C]; A61K0047-34 [I,A]; A61K0047-34 [I,C]; A61K0047-38 [I,A]; A61K0047-38 [I,C]; A61K0009-00 [I,A]; A61K0009-00 [I,C]; A61K0009-48 [I,A]; A61K0009-48 [I,C]; A61K0009-52 [I,C]
MAIN/SEC.: A61K009-60
; A61K0009-66 [I,A]; A61K0009-68 [I,A]; A61K0009-68 [I,C]
BASIC ABSTRACT:

EP 215635 A UPAB: 20050424 Hard **gelatin** capsule containing a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a masticatory enhancing agent. The compsn. is liquid at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, especially 400-4000 and partic. 1000-2000. The capsule may contain up to 95 weight% active ingredient and especially up to 20%. Also the ingredient for buccal absorption may be a liquid and the carrier a solid, e.g. SiO2 or a cellulose derivative The capsule may also contain a flavouring agent. USE/ADVANTAGE - With the capsule sufficient of the active ingredient is in contact with the fluids in the buccal activity and in a form to be retained there for an effective time. They are especially useful for ingredients such as antiseptics, sore throats remedies, cold and cough prepns. and dental compsns. or for drugs to be administered by the buccal or sublingual routes when fast action, is desired with potent drugs, cardiotonic agents, e.g. without gut lumen, gut wall or hepatic first pass elimination.

MANUAL CODE: CPI: A03-C01; A12-V01; A12-W05; B04-B04A6; B04-C02D; B10-B03B; B12-A01; B12-D01; B12-F01B; B12-M11C

Member(0009)
ABEQ US 4755389 A UPAB 20050424
Hard **gelatin** capsules contains a chewable compsn. comprising (a) a semi-solid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier; and (b) a masticatory enhancing agent. Chewable compsn. is liq. at less than 1-0 deg. C.
Pref. (b) is a stabilising or suspending agent, esp. Xanthan gum. Carrier is a polyethylene glycol of mol. wt. 200-10,000. Compsn. comprises 95 wt.% or less of active ingredient.
USE - For contg. a cardioactive drug or analgesic drug as active ingredient in unit dosage form, for retention in the buccal cavity for an effective length of time. (3pp)t

Member(0015)
ABEQ RU 2018305 C1 UPAB 20050424
Hard **gelatin** capsule contg. a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a

masticatory enhancing agent. The compsn. is liq. at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, esp. 400-4000 and partic. 1000-2000. The capsule may contain up to 95 wt.% active ingredient and esp. up to 20%. Also the ingredient for buccal absorption may be a liq. and the carrier a solid, e.g. SiO2 or a cellulose deriv. The capsule may also contain a flavouring agent.

USE/ADVANTAGE - With the capsule sufficient of the active ingredient is in contact with the fluids in the buccal activity and in a form to be retained there for an effective time. They are esp. useful for ingredients such as antiseptics, sore throats remedies, cold and cough prepns. and dental compsns. or for drugs to be administered by the buccal or sublingual routes when fast action, is desired with potent drugs, cardiotonic agents, e.g. without gut lumen, gut wall or hepatic first pass elimination.

Member(0018)

ABEQ JP 96009535 B2 UPAB 20050424

Hard **gelatin** capsule contg. a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a masticatory enahncing agent. The compsn. is liq. at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, esp. 400-4000 and partic. 1000-2000. The capsule may contain up to 95 wt.% active ingredient and esp. up to 20%. Also the ingredient for buccal absorption may be a liq. and the carrier a solid, e.g. SiO2 or a cellulose deriv. The capsule may also contain a flavouring agent.

USE/ADVANTAGE - With the capsule sufficient of the active ingredient is in contact with the fluids in the buccal activity and in a form to be retained there for an effective time. They are esp. useful for ingredients such as antiseptics, sore thorats remedies, cold and cough prepns. and dental compsns. or for drugs to be administered by the buccal or sublingual routes when fast action, is desired with potent drugs, cardiotonic agents, e.g. without gut lumen, gut wall or hepatic first pass elimination.

TI Hard **gelatin** capsule containing chewable compsn. - comprises semi-solid ingredient, carrier and masticatory enhancing agent for buccal absorption or sublingual admin.

TT TT: HARD **GELATIN** CAPSULE CONTAIN CHEW COMPOSITION COMPRISE SEMI SOLID INGREDIENT CARRY MASTICATION ENHANCE AGENT BUCCAL ABSORB ADMINISTER

ALE Hard **gelatin** capsule contg. a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a masticatory enhancing agent. The compsn. is liq. at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, esp. 400-4000 and partic. 1000-2000. The capsule may contain up to 95 wt.% active ingredient and esp. up to 20%. Also the ingredient for buccal absorption may be a liq. and the carrier a solid, e.g. SiO2 or a cellulose deriv. The capsule may also contain a flavouring agent.

IT UPIT 20050424

102290-CMP 102290-USE; 103563-CMP 103563-USE; 104827-CMP 104827-USE; **108879-CMP 108879-USE**; 130269-USE; 138321-USE; 153655-CMP; 6754-CMP; 87874-CMP 87874-USE; 87878-USE

CMC UPB 20050424

DRN: 0034-U **0050-U** 0280-U 1230-U 1324-U
DCR: 102290-U 103563-U 104827-U **108879-U** 130269-U 138321-U
87874-U 87878-U
M1 *05* M423 M431 M782 R031 V751 M903
M1 *06* M423 M431 M782 Q620 R031 V735 M903
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DCN: R01324-M
DCR: 104827-M
M2 *02* D013 D021 D022 D030 E160 H1 H181 H2 H201 H4 H401 H441 H7 H721 H8 M210 M211 M215 M232 M240 M273 M281 M282 M320 M412 M431 M511 M520 M530 M540 M782 P411 R031 M903 M904 M910
RIN: 03535
DCN: R01230-M
DCR: 103563-M
M2 *03* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 R031 M903 M904 M910
DCN: **R00050-M**
DCR: **108879-M**
M2 *04* G011 G100 J0 J012 J1 J131 J2 J241 M210 M211 M262 M281 M320 M414 M431 M510 M520 M531 M540 M782 P411 R031 M903 M904 M910
DCN: R00034-M
DCR: 87874-M
M2 *09* D011 D012 E500 G010 G100 H2 H201 H4 H401 H481 H8 J0 J011 J2 J221 M210 M211 M273 M281 M312 M321 M332 M343 M371 M391 M412 M431 M511 M520 M531 M540 M640 M782 R031 V0 V411 M903 M904
DCN: R06119-M
DCR: 153655-M
M2 *10* F012 F013 F014 F015 F016 F432 G011 G100 H3 H341 J0 J012 J2 J212 M1 M113 M210 M211 M240 M272 M282 M320 M413 M431 M510 M521 M531 M540 M782 P522 R031 M903 M904
DCN: R03027-M
DCR: 6754-M
M5 *08* M431 M782 P625 R031 S004 S110 S132 S133 S134 S142 S143 S217 S317 S517 S603 T917 U017 U035 U520 U521 M903 M904 M910
DCN: R00280-M
DCR: 102290-M
M6 *07* P220 P411 P447 P522 P625 P821 P923 Q620 R031 R111 R200 R315 R320 M903

DRN 0034-U **0050-U** 0280-U 1230-U 1324-U
M2 *03* G017 G019 G100 H1 H100 H181 H4 H401 H441 H5 H541 H6 H604 H609 H643 H8 J0 J011 J1 J171 M1 M121 M141 M280 M312 M321 M332 M343 M349 M371 M391 M414 M431 M510 M520 M532 M540 M782 R031 M903 M904 M910
DCN: **R00050-M**
DCR: **108879-M**

Member(0009)
ABEQ US 4755389 A UPAB 20050424
Hard **gelatin** capsules contains a chewable compsn. comprising (a) a semi-solid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier; and (b) a masticatory enhancing agent. Chewable compsn. is liq. at less than 1-0 deg. C.

Pref. (b) is a stabilising or suspending agent, esp. Xanthan gum. Carrier is a polyethylene glycol of mol. wt. 200-10,000. Compsn. comprises 95 wt.% or less of active ingredient.

USE - For contg. a cardioactive drug or analgesic drug as active ingredient in unit dosage form, for retention in the buccal cavity for an effective length of time. (3pp)t

Member(0015)
ABEQ RU 2018305 C1 UPAB 20050424

Hard **gelatin** capsule contg. a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a masticatory enhancing agent. The compsn. is liq. at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, esp. 400-4000 and partic. 1000-2000. The capsule may contain up to 95 wt.% active ingredient and esp. up to 20%. Also the ingredient for buccal absorption may be a liq. and the carrier a solid, e.g. SiO2 or a cellulose deriv. The capsule may also contain a flavouring agent.

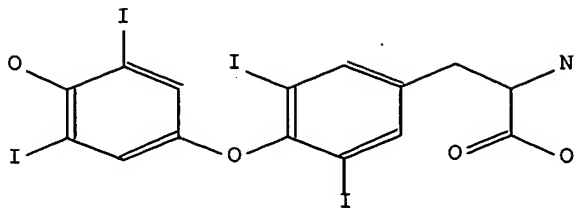
USE/ADVANTAGE - With the capsule sufficient of the active ingredient is in contact with the fluids in the buccal activity and in a form to be retained there for an effective time. They are esp. useful for ingredients such as antiseptics, sore throats remedies, cold and cough prepns. and dental compsns. or for drugs to be administered by the buccal or sublingual routes when fast action, is desired with potent drugs, cardiotonic agents, e.g. without gut lumen, gut wall or hepatic first pass elimination.

Member(0018)
ABEQ JP 96009535 B2 UPAB 20050424

Hard **gelatin** capsule contg. a chewable compsn. comprises (a) a semisolid compsn. comprising an ingredient for buccal absorption or having buccal activity in association with a non-toxic carrier and (b) a masticatory enahncing agent. The compsn. is liq. at below 100 deg. C. Pref. the carrier may be semi-solid. The masticatory enhancing agent may be a stabilising or suspending agent, e.g. a gum such as xanthan gum. The carrier may be polyethylene glycol 200-10000, esp. 400-4000 and partic. 1000-2000. The capsule may contain up to 95 wt.% active ingredient and esp. up to 20%. Also the ingredient for buccal absorption may be a liq. and the carrier a solid, e.g. SiO2 or a cellulose deriv. The capsule may also contain a flavouring agent.

USE/ADVANTAGE - With the capsule sufficient of the active ingredient is in contact with the fluids in the buccal activity and in a form to be retained there for an effective time. They are esp. useful for ingredients such as antiseptics, sore thorats remedies, cold and cough prepns. and dental compsns. or for drugs to be administered by the buccal or sublingual routes when fast action, is desired with potent drugs, cardiotonic agents, e.g. without gut lumen, gut wall or hepatic first pass elimination.

AN.S DCR-108879
CN.P THYROXINE
CN.S 2-Amino-3-[4-(4-hydroxy-3,5-diiodo-phenoxy)-3,5-diiodo-phenyl]-propionic acid
SDCN R00050; R04769
SDRN 0050



L86 ANSWER 35 OF 40 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1966-34553F [00] WPIX
TITLE: **Thyroxine** compns contng an electrically charged
DERWENT CLASS: B04
PATENT ASSIGNEE: (ISRA-I) ISRAEL; (ISRE-C) ISRAEL M
COUNTRY COUNT: 3

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
FR 6191	M		(196800)*	FR		
GB 1180574	A		(197005)	EN		
DE 1617540	A	19710408	(198448)	DE		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

PRIORITY APPLN. INFO: MX 1966-87206 19660218
INT. PATENT CLASSIF.:
MAIN/SEC.: A61K000-00
BASIC ABSTRACT:
FR 6191 M UPAB: 20050412
Thyroxine compns. contng. an electrically charged macromolecular cpd. and calcium gluconate. For parenteral administration of **thyroxine** in high and frequent doses.
The pref. macromolecular cpd. is a combination of vitamin B12 and **gelatine**, the latter being in a considerable excess. A pref. composition contains 0.5 mg. vitamin B12, 0.5 mg. sodium **thyroxine**, 10 mg. **gelatine**, and 100 mg. calcium gluconate, in a physiological serum (e.g. 0.9% NaCl). MANUAL CODE: CPI: B03-E; B04-B04A; B04-C02; B05-A01B; B10-A07; B10-B02B; B12-H03
TI **Thyroxine** compns contng an electrically charged
TT TT: **THYROXINE** ELECTRIC CHARGE
ALE **Thyroxine** compns. contng. an electrically charged macromolecular cpd. and calcium gluconate.
For parenteral administration of **thyroxine** in high and frequent doses.
The pref. macromolecular cpd. is a combination of vitamin B12 and **gelatine**, the latter being in a considerable excess. A pref. compn. contains 0.5 mg. vitamin B12, 0.5 mg. sodium **thyroxine**, 10 mg. **gelatine**, and 100 mg. calcium gluconate, in a physiological serum (e.g. 0.9% NaCl).
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L86 ANSWER 36 OF 40 TOXCENTER COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1992:131738 TOXCENTER Full-text
COPYRIGHT: Copyright 2007 ACS
DOCUMENT NUMBER: CA11616158934F
TITLE: Plant pigments as light stabilizers for **photosensitive** drugs
AUTHOR(S): Nagy Kricsfalussy, Margit; Balazs, Rita; Marcisz, Judit; Wagner Nagy, Katalin; Tajthy Juhasz, Eva Judit; Mandi, Attila; Csorgo, Margit
CORPORATE SOURCE: ASSIGNEE: EGIS Gyogyszergyar
PATENT INFORMATION: DE 4124081 A1 23 Jan 1992
SOURCE: (1992) Ger. Offen., 10 pp.
CODEN: GWXXBX.
COUNTRY: HUNGARY
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1992:158934
LANGUAGE: German
ENTRY DATE: Entered STN: 16 Nov 2001
Last Updated on STN: 8 Oct 2002

ABSTRACT:
Light-sensitive insol. drugs are stabilized in solid formulations by plant pigments, such as chlorophyll, caramel, saffron yellow and red beet pigment. ***Gelatin*** capsules were filled with a mixture of nifedipine 3.00, poly(ethylene oxide) sorbitan monooleate 22.85, lemon oil 14.65, lecithin 57.00, and chlorophyll 2.50% by weight

CLASSIFICATION CODE: 63-6
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
photostabilizer drug plant pigment
REGISTRY NUMBER: 50-53-3 (Chlorpromazine)
51-48-9 (**Levothyroxine**)
51-61-6 (Dopamine)
52-86-8 (Haloperidol)
53-21-4 (Cocaine hydrochloride)
54-05-7 (Chloroquine)
55-63-0 (Nitroglycerine)
57-27-2Q (Morphine, derivs.)
59-05-2 (Methotrexate)
60-56-0 (Methimazol)
61-25-6 (Papaverine hydrochloride)
62-49-7Q (amino derivs.)
64-31-3 (Morphine sulfate)
64-86-8 (Colchicine)
67-20-9 (Nitrofurantoin)
67-97-0 (Cholecalciferol)
68-35-9 (Sulfadiazine)
91-81-6 (Tripelenamine)
92-84-2Q (Phenthiazine, derivs.)
107-15-3Q (Ethylene diamine, derivs.)
110-85-0Q (Piperazine, derivs.)
117-89-5 (Trifluoperazine)
298-46-4 (Carbamazepine)
378-44-9 (Betamethasone)
446-86-6 (Azathioprine)
495-40-9Q (Butyrophenone, derivs.)
548-73-2 (Droperidol)
671-16-9 (Procarbazine)
1404-00-8 (Mitomycin)

1405-87-4 (Bacitracin)
2062-84-2 (Benperidol)
8067-24-1 (Dihydroergotoxin methanesulfonate)
11103-57-4 (Vitamin A)
14402-89-2 (Nitroprusside sodium)
21829-25-4 (Nifedipine)
22609-73-0 (Niludipine)
27194-24-7Q (Nitrofuran, derivs.)
27790-75-6Q (Dihydropyridine, derivs.)
28299-33-4Q (Imidazoline, derivs.)
39562-70-4 (Nitrendipine)
55985-32-5 (Nicardipine)
63675-72-9 (Nisoldipine)
66085-59-4 (Nimodipine)
72509-76-3 (Felodipine)
REGISTRY NUMBER: 550-70-9; 5635-50-7; 22071-15-4; 139755-07-0

L86 ANSWER 37 OF 40 TOXCENTER COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1971:47168 TOXCENTER Full-text
COPYRIGHT: Copyright 2007 ACS
DOCUMENT NUMBER: CA07402006253J
TITLE: Utilization of **slaughterhouse** wastes and by-products
AUTHOR(S): Wahid, Mukhtar A.
CORPORATE SOURCE: Biochem. Res. Div., PCSIR Lab., Karachi, Pak..
SOURCE: Science and Industry (Karachi), (1970) Vol. 7, No. 1-2, pp. 7-14.
CODEN: SINDBP. ISSN: 0036-8199.
COUNTRY: PAKISTAN
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1971:6253
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 2001
Last Updated on STN: 24 Dec 2002
ABSTRACT:
Manufacture of biochems. such as heparin, cholesterol, cholic acids, rennin, pancreatin, pepsin, dry thyroid extract, **thyroxine**, insulin, K ferricyanide and ferrocyanide, adrenaline, ACTH, hyaluronidase, catalase, trypsin, **gelatin**, chymotrypsin, etc., from the wastes of slaughterhouse are described. 42 refs.
CLASSIFICATION CODE: 60
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
review slaughterhouse wastes pharmaceuticals; slaughterhouse wastes pharmaceuticals review; pharmaceuticals slaughterhouse wastes review

L86 ANSWER 38 OF 40 TOXCENTER COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1970:46699 TOXCENTER Full-text
COPYRIGHT: Copyright 2007 ACS
DOCUMENT NUMBER: CA07206024635Y
TITLE: Compositions for **parenteral** administration of **thyroxine**
AUTHOR(S): Israel, Murray
PATENT INFORMATION: FR 6191 26 Aug 1968
SOURCE: (1968) Fr. M., 3 pp.
CODEN: FMXXAJ.
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1970:24635

LANGUAGE: French
ENTRY DATE: Entered STN: 16 Nov 2001
Last Updated on STN: 31 Dec 2002
ABSTRACT:
The title injectible compns. for treating hypercholesterolemia, hyperventilation, and disequilibrated metabolisms were prepared by adding to 100 ml of a 1% aqueous **gelatin** solution 50 mg crystalline vitamin B12, 50 mg. ***thyroxine*** sodium salt, and 10 g. Ca gluconate at ambient temperature and pH
7, stirring vigorously, sterilizing, and sealing in amber glass ampuls. The dose is 1 ml for parenteral administration. The long therapeutic use of this medicament did not show any thyrotoxicity signs.
CLASSIFICATION CODE: 63
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
thyroxines parenteral compn; hypercholesterolemia; hyperventilation; metabolism disequilibrated drugs
REGISTRY NUMBER: **55-03-8**

L86 ANSWER 39 OF 40 TOXCENTER COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1962:17537 TOXCENTER Full-text
COPYRIGHT: Copyright 2007 ACS
DOCUMENT NUMBER: CA05705029953A
TITLE: Compositions and method for the **parenteral** administration of **thyroxine**
AUTHOR(S): Israel, Murray
PATENT INFORMATION: US 3035974 22 May 1962
SOURCE: (1962)
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1962:429953
ENTRY DATE: Entered STN: 16 Nov 2001
Last Updated on STN: 5 Dec 2006
ABSTRACT:
This composition for the parenteral therapeutic use of **thyroxine** (I) consists of an aqueous medium containing >0.06 mg./ml. of a water-soluble salt of I, and
also vitamin B12 (II) and **gelatin** (III), III being present in an amount greater than the II, and the II and III together having at least 5 times the weight of the I. Both II and III are associated with each other in the form of a macroanionic substance in dispersed phase and having a mol. weight of at least 100,000. Thus, 100 ml. of a 1% aqueous solution of III was produced by autoclaving an
aqueous dispersion of 1 g. of III; then 50 mg. each of crystalline II and Na DL-I were
added. At room temperature and a pH of 7, the mixture was vigorously agitated. After
sterilization of the solution by Seitz filtration, it was sealed in amber ampuls. Prolonged therapy may be conducted with this composition, with no evidence of thyrotoxicity, yet maintaining human blood cholesterol levels at low and narrow ranges for long periods of time without relapse.
CLASSIFICATION CODE: 39
REGISTRY NUMBER: 51-48-9 (**Thyroxine**)

L86 ANSWER 40 OF 40 SCISEARCH COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:311725 SCISEARCH Full-text
THE GENUINE ARTICLE: WU640
TITLE: Stability-indicating high-performance liquid chromatographic assay methods for drugs in **pharmaceutical** dosage forms .2.

AUTHOR: Ho C (Reprint); Chen G L
CORPORATE SOURCE: DEPT HLTH, NATL LABS FOODS & DRUGS, TAIPEI, TAIWAN; NATL DEF MED CTR, SCH PHARM, TAIPEI, TAIWAN
COUNTRY OF AUTHOR: TAIWAN
SOURCE: JOURNAL OF FOOD AND DRUG ANALYSIS, (MAR 1997) Vol. 5, No. 1, pp. 1-24.
ISSN: 1021-9498.
PUBLISHER: NATL LABORATORIES FOODS DRUGS, DEPT HEALTH, EXECUTIVE YUAN, 161-2 KUEN YANG ST DR. ERICK T. SUEN, DEPUTY DIR., NANKANG, TAIPEI, TAIWAN.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 93
ENTRY DATE: Entered STN: 1997
Last Updated on STN: 1997
CATEGORY: FOOD SCIENCE & TECHNOLOGY; PHARMACOLOGY & PHARMACY
SUPPL. TERM PLUS: SOFT **GELATIN** CAPSULES; REVERSED-PHASE HPLC; DEGRADATION PRODUCTS; DILTIAZEM HYDROCHLORIDE; OPHTHALMIC PREPARATIONS; DECOMPOSITION PRODUCTS; PRALIDOXIME CHLORIDE; SODIUM **LEVOTHYROXINE**; TABLET FORMULATIONS; CONTENT UNIFORMITY

REFERENCE(S):

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	ARN PG (RPG)	Referenced Work (RWK)
ABDELHAMID M E	1988	21	2263	ANAL LETT
ALBERT K	1985	130	2600	PHARM ZTG
ALVI S U	1987	10	3413	J LIQ CHROMATOGR
AMIN M	1989	64	45	PHARM ACTA HELV
ANDERMANN G	1984	298	189	J CHROMATOGR
BAASKE D M	1979	68	481	J PHARM SCI
BACHMAN W J	1990	23	893	ANAL LETT
BALANSARD G	1986	61	47	PHARM ACTA HELV
BAMMI R K	1991	17	2239	DRUG DEV IND PHARM
BARRETT D A	1994	17	3727	J LIQ CHROMATOGR
BAUER J	1986	369	422	J CHROMATOGR
BAUER J	1988	445	429	J CHROMATOGR
BAUER J	1983	72	924	J PHARM SCI
BAUER J	1983	72	1347	J PHARM SCI
BRIDLE J H	1993	19	371	DRUG DEV IND PHARM
BUCK R H	1991	548	335	J CHROMATOGR
CARIGNAN G	1985	8	1431	J LIQ CHROMATOGR
CAVIGLIOLI G	1994	20	2395	DRUG DEV IND PHARM
CHI H	1984	4	339	YAOWU FENXI ZAZHI
DASGUPTA V	1986	9	1065	J LIQ CHROMATOGR
DASGUPTA V	1983	72	1453	J PHARM SCI
DESCHUTTER J A	1985	20	185	CHROMATOGRAPHIA
ELSAYEDMETWALLY M	1991	549	221	J CHROMATOGR
FATMI A A	1989	15	1365	DRUG DEV IND PHARM
FRONTINI R	1992	15	2519	J LIQ CHROMATOGR
GARNICK R L	1984	73	75	J PHARM SCI
HEIDEMANN D R	1987	5	422	LC GC
HEWALA I I	1994	27	71	ANAL LETT
HITSCHERICH M E	1987	10	1011	J LIQ CHROMATOGR
HOYER G L	1995	18	1239	J LIQ CHROMATOGR
HU O Y P	1990	523	321	J CHROMATOGR
HU O Y P	1992	81	91	J PHARM SCI
IRWIN W J	1984	9	41	J CLIN HOSP PHARM
KAFIL J B	1994	667	175	J CHROMATOGR A
KENLEY R	1986	9	3577	J LIQ CHROMATOGR

KENNEDY J F	1989	5	281	J MICRONUTR ANAL
KHALIL S A H	1993	26	1163	ANAL LETT
KIRCHHOEFER R D	1985	68	163	J ASSOC OFF ANA CHEM
KMETEC V	1992	10	1073	J PHARMACEUT BIOMED
LAI C J	1993	45	147	CHUNG HUA YAO HSUEH
LEE Y C	1984	73	1660	J PHARM SCI
LEROY P	1986	367	428	J CHROMATOGR
LIAN H	1989	9	197	YAOWU FENXI ZAZHI
LIU C Y	1993	13	314	YAOWU FENXI ZAZHI
MALKKI L	1993	11	79	J PHARMACEUT BIOMED
MELUCCI C K	1987	391	321	J CHROMATOGR
MENON S K	1989	12	657	J LIQ CHROMATOGR
MENSINK C K	1987	122	385	PHARM WEEKBLAD
PARASRAMPURIA J	1989	15	1989	DRUG DEV IND PHARM
PARHIZKARI G	1995	18	553	J LIQ CHROMATOGR
PAVEENBAMPEN C	1986	75	1192	J PHARM SCI
PAVELEK Z	1988	37	32	CESK FARM
PERLMAN S	1984	73	259	J PHARM SCI
PRUE D G	1983	72	751	J PHARM SCI
REIF V D	1987	4	54	PHARMACEUT RES
RENZI N L	1989	462	398	J CHROMATOGR
RICHARD A	1984	298	356	J CHROMATOGR
RICHHEIMER S L	1983	72	1349	J PHARM SCI
RILEY C M	1993	11	131	J PHARMACEUT BIOMED
SALEM M A S	1989	22	2501	ANAL LETT
SCHROEDER A C	1989	78	132	J PHARM SCI
SHEN Y	1994	17	1557	J LIQ CHROMATOGR
SHIVRAM K	1992	15	2417	J LIQ CHROMATOGR
SISCO W R	1985	322	380	J CHROMATOGR
SISCO W R	1985	348	253	J CHROMATOGR
SISCO W R	1986	354	355	J CHROMATOGR
SISCO W R	1986	368	184	J CHROMATOGR
SMITH E W	1989	6	431	PHARMACEUT RES
SOTBERSKI P	1987	43	407	FARM POL
STEWART J T	1989	12	673	J LIQ CHROMATOGR
STOBERSKI P	1988	44	398	FARM POL
SUBBARAO G N	1987	4	38	PHARMACEUT RES
SULEIMAN M S	1989	22	1499	ANAL LETT
SULEIMAN M S	1989	114	365	ANALYST
TENJARLA S N	1993	16	2899	J LIQ CHROMATOGR
TOKUNAGA H	1984	33	26	BUNSEKI KAGAKU
TOROK I	1984	2	465	J PHARM BIOMED ANAL
TRIVEDI R J	1988	71	36	J ASSOC OFF ANA CHEM
TRIVEDI R J	1988	71	290	J ASSOC OFF ANA CHEM
TSAI T H	1992	84	279	INT J PHARM
TSAI T H	1991	542	521	J CHROMATOGR
UNLU N	1987	7	1	ECZACILIK FAK DERG
WALL G M	1992	10	465	J PHARMACEUT BIOMED
WANG D P	1983	108	851	ANALYST
WANG S	1991	11	81	YAOWU FENXI ZAZHI
WANWIMOLRUK S	1991	8	547	PHARMACEUT RES
WILSON T D	1987	391	409	J CHROMATOGR
WILSON T D	1988	445	299	J CHROMATOGR
WU S	1993	45	133	CHUNG HUA YAO HSUEH
WU S C	1995	47	457	CHUNG HUA YAO HSUEH
YAMAMOTO S	1993	113	515	YAKUGAKU ZASSHI
YAMAMURA K	1984	303	165	J CHROMATOGR
ZADRZEWSKI Z	1990	46	19	FARM POL

FILE 'HOME' ENTERED AT 12:45:49 ON 23 FEB 2007

SEARCH HISTORY

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=> d his nofile

     (FILE 'HOME' ENTERED AT 11:49:29 ON 23 FEB 2007)

     FILE 'CAPLUS' ENTERED AT 11:50:20 ON 23 FEB 2007
                E US2003-661588/APPS
L1              1 SEA ABB=ON  US2003-661588/AP
                D SCAN
L2             13 SEA ABB=ON  SCHREDER S?/AU
L3              2 SEA ABB=ON  NISCHWITZ M?/AU
L4              2 SEA ABB=ON  L2 AND L3
                D SCAN TI

     FILE 'REGISTRY' ENTERED AT 11:51:53 ON 23 FEB 2007
                E LEVOTHYROXINE SODIUM/CN
L5              1 SEA ABB=ON  "LEVOTHYROXINE SODIUM"/CN

     FILE 'REGISTRY' ENTERED AT 11:52:37 ON 23 FEB 2007
                D IDE

     FILE 'CAPLUS' ENTERED AT 11:54:13 ON 23 FEB 2007
L6            488 SEA ABB=ON  L5
L7              2 SEA ABB=ON  (L2 OR L3) AND L6
L8              2 SEA ABB=ON  L7 AND L4
L9          41163 SEA ABB=ON  GELATIN#/OBI
L10            11 SEA ABB=ON  L6 AND L9
L11          6587 SEA ABB=ON  L9(L)(PAC OR PKT OR DMA OR THU)/RL
L12            10 SEA ABB=ON  L11 AND L6

     FILE 'MEDLINE' ENTERED AT 11:58:00 ON 23 FEB 2007
L13         28884 SEA ABB=ON  THYROXINE/CT
L14          5986 SEA ABB=ON  GELATIN/CT
L15             3 SEA ABB=ON  L13 AND L14
L16             3 SEA ABB=ON  SCHREDER S?/AU
L17             0 SEA ABB=ON  NISCHWITZ M?/AU
                D TRIAL L16 1-3
L18             3 SEA ABB=ON  (L16 OR L17)
                D TRIAL L15 1-3
L19          9914 SEA ABB=ON  L13(L)(AD OR PD OR PK OR TU)/CT
L20             2 SEA ABB=ON  L19 AND L14
L21         14972 SEA ABB=ON  GELATIN#
L22             5 SEA ABB=ON  L19 AND L21
L23             3 SEA ABB=ON  L22 NOT L15
                D TRIAL 1-3

     FILE 'EMBASE' ENTERED AT 12:01:25 ON 23 FEB 2007
L24             7 SEA ABB=ON  SCHREDER S?/AU
L25             0 SEA ABB=ON  NISCHWITZ M?/AU
L26          1269 SEA ABB=ON  L5
                D TRIAL 1-6
L27          1268 SEA ABB=ON  LEVOTHYROXINE SODIUM/CT
L28            64 SEA ABB=ON  L27(L)CB/CT
                E GELATIN/CT
                E E3+ALL
L29          6703 SEA ABB=ON  GELATIN/CT
L30             0 SEA ABB=ON  L27 AND L29 NOT L28
L31             0 SEA ABB=ON  L27 AND L29
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```
L32        13468 SEA ABB=ON  GELATIN#
L33            0 SEA ABB=ON  L27 AND L32
L34            0 SEA ABB=ON  (L26 OR L27) AND (L29 OR L32)
L35            7 SEA ABB=ON  (L24 OR L25)

     FILE 'DRUGU' ENTERED AT 12:03:55 ON 23 FEB 2007
L36            3 SEA ABB=ON  SCHREDER S?/AU
L37            0 SEA ABB=ON  NISCHWITZ M?/AU
                 D TRIAL L36 1-3
L38            3 SEA ABB=ON  (L36 OR L37)
L39          439 SEA ABB=ON  L5
                 D TRIAL 1-5
L40         1142 SEA ABB=ON  LEVOTHYROXINE SODIUM/CT
L41         3909 SEA ABB=ON  GELATIN#
L42            0 SEA ABB=ON  (L39 OR L40) AND L41

     FILE 'WPIX' ENTERED AT 12:06:20 ON 23 FEB 2007
L43            7 SEA ABB=ON  SCHREDER S?/AU
L44            2 SEA ABB=ON  NISCHWITZ M?/AU
                 D TRIAL 1-2
                 E B04-N02+ALL/MC
                 E B10-B02E+ALL/MC
                 E B12-M11B+ALL/MC
                 E B14-N11+ALL/MC
L45           72 SEA ABB=ON  (LEVOTHYROXINE/BI,ABEX OR (LEVO/BI,ABEX OR
                 L/BI,ABEX)(W)THYROXINE/BI,ABEX)(1A)(MONOSODIUM/BI,ABEX OR
                 NA/BI,ABEX OR SODIUM/BI,ABEX) OR NSC259940/BI,ABEX OR NSC
                 259940/BI,ABEX
L46          802 SEA ABB=ON  LEVOTHYROXIN#/BI,ABEX OR THYROXIN#/BI,ABEX
                 E LEVOTHYR/CN
L47            2 SEA ABB=ON  ("LEVOTHYROXINE SODIUM"/CN OR LEVOTHYROXINE-SODIUM/
                 CN)
L48          540 SEA ABB=ON  L47/DCR
                 SEL SDRN,SDCN,DCSE L47
L49          540 SEA ABB=ON  (RA11AM/DRN,DCN,DCRE OR R00050/DRN,DCN,DCRE OR
                 R04769/DRN,DCN,DCRE OR 0050/DRN,DCN,DCRE OR 108879-0-0-0/DRN,DC
                 N,DCRE OR 108879-2-0-0/DRN,DCN,DCRE)
L50         1021 SEA ABB=ON  (L49 OR L48 OR L46 OR L45)
L51        34560 SEA ABB=ON  GELATIN#/BI,ABEX
L52            2 SEA ABB=ON  (L43 AND L44) OR ((L43 OR L44) AND L50)
L53           41 SEA ABB=ON  L50 AND L51
L54           39 SEA ABB=ON  L53 NOT L52
                 D TRIAL 1-39

     FILE 'STNGUIDE' ENTERED AT 12:12:36 ON 23 FEB 2007

     FILE 'WPIX' ENTERED AT 12:13:52 ON 23 FEB 2007
L55        15426 SEA ABB=ON  ?ASSAY?/TI
L56       199868 SEA ABB=ON  MEASURING/TI
L57           30 SEA ABB=ON  L54 NOT (L55 OR L56)
                 D TRIAL 1-30

     FILE 'STNGUIDE' ENTERED AT 12:14:24 ON 23 FEB 2007

     FILE 'WPIX' ENTERED AT 12:17:35 ON 23 FEB 2007
L58        14807 SEA ABB=ON  ANALYZING/TI
L59       318260 SEA ABB=ON  SIMULTANEOUS?/BI,ABEX
L60        14807 SEA ABB=ON  ANALYZING/TI
L61        61970 SEA ABB=ON  SIMULTANEOUS?/TI
L62           30 SEA ABB=ON  L53 NOT (L55 OR L56 OR L60 OR L61)
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     FILE 'IPA' ENTERED AT 12:19:02 ON 23 FEB 2007
L63            2 SEA ABB=ON  SCHREDER S?/AU
L64            0 SEA ABB=ON  NISCHWITZ M?/AU
                 D TRIAL L63 1-2
L65            2 SEA ABB=ON  (L63 OR L64)
L66            1 SEA ABB=ON  L5
L67          798 SEA ABB=ON  (LEVOTHYROXINE OR THYROXINE) OR NSC259940 OR NSC
                 259940
L68         1409 SEA ABB=ON  GELATIN#
L69            0 SEA ABB=ON  (L66 OR L67) AND L68
L70         6117 SEA ABB=ON  GEL?
L71            5 SEA ABB=ON  (L66 OR L67) AND L70
                 D TRIAL 1-5

     INDEX '1MOBILITY, 2MOBILITY, ABI-INFORM, ADISCTI, AEROSPACE, AGRICOLA,
     ALUMINIUM, ANABSTR, ANTE, APOLLIT, AQUALINE, AQUASCI, AQUIRE, BABS,
     BIBLIODATA, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CAOLD, CAPLUS, CASREACT, CBNB, CEABA-VTB, CERAB, ...' ENTERED AT 12:22:12
     ON 23 FEB 2007
               SEA (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC 259940) AND
              ---------
               1    FILE ABI-INFORM
               1    FILE AGRICOLA
               6    FILE ANABSTR
               1    FILE AQUASCI
               1    FILE AQUIRE
               1    FILE BABS
              10    FILE BIOSIS
               1    FILE BIOTECHNO
               4    FILE CABA
               3    FILE CAOLD
              39    FILE CAPLUS
               1    FILE CASREACT
               2    FILE CROPU
               3    FILE DDFB
               1    FILE DDFU
               1    FILE DPCI
               3    FILE DRUGB
               1    FILE DRUGU
              20    FILE EMBASE
                SEA (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC 259940 OR L
              ---------
               0*   FILE 1MOBILITY
               0*   FILE 2MOBILITY
               1    FILE ABI-INFORM
               0*   FILE ADISCTI
               0*   FILE AEROSPACE
               1    FILE AGRICOLA
               0*   FILE ALUMINIUM
               6    FILE ANABSTR
               0*   FILE ANTE
               0*   FILE APOLLIT
               0*   FILE AQUALINE
               1*   FILE AQUASCI
               1    FILE AQUIRE
               1*   FILE BABS
               0*   FILE BIBLIODATA
               0*   FILE BIOENG
              10    FILE BIOSIS
```

```
  1    FILE BIOTECHNO
  4*   FILE CABA
  3*   FILE CAOLD
 39*   FILE CAPLUS
  1    FILE CASREACT
  0*   FILE CEABA-VTB
  0*   FILE CERAB
  0*   FILE CHEMINFORMRX
  0*   FILE CIVILENG
  0*   FILE COMPENDEX
  0*   FILE COMPUAB
  0*   FILE COMPUSCIENCE
  0*   FILE CONFSCI
  0*   FILE COPPERLIT
  0*   FILE CORROSION
  0*   FILE CROPB
  2*   FILE CROPU
  3*   FILE DDFB
  1*   FILE DDFU
  0*   FILE DETHERM
  0*   FILE DGENE
  0*   FILE DISSABS
  0*   FILE DKF
  1*   FILE DPCI
  3*   FILE DRUGB
  1*   FILE DRUGU
  0*   FILE ELCOM
  0*   FILE EMBAL
 20    FILE EMBASE
  0*   FILE ENCOMPLIT
  0*   FILE ENCOMPPAT
  2*   FILE ENERGY
  0*   FILE ENVIROENG
389*   FILE EPFULL
  1*   FILE ESBIOBASE
  0*   FILE FOMAD
  0*   FILE FORIS
  0*   FILE FRANCEPAT
 18*   FILE FRFULL
  0*   FILE FROSTI
  1    FILE FSTA
 37*   FILE GBFULL
  0*   FILE GENBANK
  0*   FILE GEOREF
  0*   FILE HEALSAFE
  0*   FILE ICONDA
 31*   FILE IFIPAT
  0*   FILE INFODATA
  1*   FILE INIS
  8*   FILE INPADOC
  0*   FILE INSPEC
  0*   FILE INSPHYS
  0*   FILE ITRD
  1*   FILE JAPIO
  0*   FILE KOREAPAT
  0*   FILE KOSMET
  1*   FILE LIFESCI
  0*   FILE LISA
  0*   FILE MATBUS
  0*   FILE MECHENG
```

```
                9   FILE MEDLINE
                0*  FILE METADEX
                0*  FILE NTIS
                0*  FILE NUTRACEUT
                0*  FILE OCEAN
                2*  FILE PASCAL
                0*  FILE PATDD
                0*  FILE PATDPA
               10*  FILE PATDPAFULL
             1385*  FILE PCTFULL
                0*  FILE PCTGEN
                0*  FILE PHARMAML
                0*  FILE PHIC
                0*  FILE PHIN
                0*  FILE POLLUAB
                1   FILE PROMT
                3*  FILE RDISCLOSURE
                0*  FILE RSWB
                1*  FILE RUSSIAPAT
                8*  FILE SCISEARCH
                0*  FILE SOLIDSTATE
                0*  FILE SOLIS
                0*  FILE TEMA
                0*  FILE TEXTILETECH
               19   FILE TOXCENTER
                0*  FILE TRIBO
                0*  FILE UFORDAT
             2491*  FILE USPATFULL
              259*  FILE USPAT2
                0*  FILE VETB
                2*  FILE VETU
                0*  FILE WATER
                0*  FILE WELDASEARCH
               34   FILE WPIDS
                0*  FILE WPIFV
               34   FILE WPINDEX
                0*  FILE WTEXTILES
L72              QUE ABB=ON  (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC
                 259940 OR L5) AND GELATIN#
                 ---------
                 D RANK

     FILE 'STNGUIDE' ENTERED AT 12:27:27 ON 23 FEB 2007

     FILE 'AGRICOLA, PASCAL, BIOTECHNO, ESBIOBASE, LIFESCI, DRUGB, BIOSIS,
     VETU, TOXCENTER, ANABSTR, SCISEARCH' ENTERED AT 12:29:32 ON 23 FEB 2007
L73            13 SEA ABB=ON  SCHREDER S?/AU
L74             2 SEA ABB=ON  NISCHWITZ M?/AU
L75         94695 SEA ABB=ON  (LEVOTHYROXINE OR THYROXINE OR NSC259940 OR NSC
                  259940 OR L5)
L76         57422 SEA ABB=ON  GELATIN#
L77             2 SEA ABB=ON  (L73 AND L74) OR ((L73 OR L74) AND L75)
                  D SCAN
L78            54 SEA ABB=ON  L75 AND L76
L79            37 DUP REM L78 (17 DUPLICATES REMOVED)
                       ANSWER '1' FROM FILE AGRICOLA
                       ANSWERS '2-3' FROM FILE PASCAL
                       ANSWER '4' FROM FILE LIFESCI
                       ANSWERS '5-7' FROM FILE DRUGB
                       ANSWERS '8-15' FROM FILE BIOSIS
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                    ANSWER '16' FROM FILE VETU
                    ANSWERS '17-28' FROM FILE TOXCENTER
                    ANSWERS '29-34' FROM FILE ANABSTR
                    ANSWERS '35-37' FROM FILE SCISEARCH
               D SCAN

     FILE 'STNGUIDE' ENTERED AT 12:31:30 ON 23 FEB 2007

     FILE 'AGRICOLA, PASCAL, BIOTECHNO, ESBIOBASE, LIFESCI, DRUGB, BIOSIS,
     VETU, TOXCENTER, ANABSTR, SCISEARCH' ENTERED AT 12:35:34 ON 23 FEB 2007
               D TI 1-37

     FILE 'STNGUIDE' ENTERED AT 12:36:09 ON 23 FEB 2007

     FILE 'AGRICOLA, PASCAL, BIOTECHNO, ESBIOBASE, LIFESCI, DRUGB, BIOSIS,
     VETU, TOXCENTER, ANABSTR, SCISEARCH' ENTERED AT 12:39:05 ON 23 FEB 2007
L80             8 SEA ABB=ON  L78 AND (SLAUGHTER? OR WOUND OR PHOTOSENSITIVE OR
                  PARENTERAL OR PHARMACEUTICAL OR MEDICAMENTS)/TI

     FILE 'STNGUIDE' ENTERED AT 12:39:19 ON 23 FEB 2007

     FILE 'CAPLUS' ENTERED AT 12:39:53 ON 23 FEB 2007
               D QUE L7

     FILE 'MEDLINE' ENTERED AT 12:39:53 ON 23 FEB 2007
               D QUE L18

     FILE 'EMBASE' ENTERED AT 12:39:53 ON 23 FEB 2007
               D QUE L35

     FILE 'DRUGU' ENTERED AT 12:39:53 ON 23 FEB 2007
               D QUE L38

     FILE 'WPIX' ENTERED AT 12:39:54 ON 23 FEB 2007
               D QUE L52

     FILE 'IPA' ENTERED AT 12:39:55 ON 23 FEB 2007
               D QUE L65

     FILE 'AGRICOLA, PASCAL, BIOTECHNO, ESBIOBASE, LIFESCI, DRUGB, BIOSIS,
     VETU, TOXCENTER, ANABSTR, SCISEARCH' ENTERED AT 12:40:06 ON 23 FEB 2007
               D QUE L77

     FILE 'MEDLINE, DRUGU, CAPLUS, IPA, WPIX, EMBASE, BIOSIS' ENTERED AT
     12:40:26 ON 23 FEB 2007
L81            12 DUP REM L18 L38 L7 L65 L52 L35 L77 (9 DUPLICATES REMOVED)
                    ANSWERS '1-3' FROM FILE MEDLINE
                    ANSWER '4' FROM FILE DRUGU
                    ANSWERS '5-6' FROM FILE CAPLUS
                    ANSWERS '7-10' FROM FILE EMBASE
                    ANSWERS '11-12' FROM FILE BIOSIS
               D IALL 1-4
               D IBIB ED ABS HITIND 5-6
               D IALL 7-12

     FILE 'STNGUIDE' ENTERED AT 12:41:09 ON 23 FEB 2007

     FILE 'CAPLUS' ENTERED AT 12:43:27 ON 23 FEB 2007
               D QUE L12
L82             8 SEA ABB=ON  L12 NOT L7
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     FILE 'EMBASE' ENTERED AT 12:43:29 ON 23 FEB 2007
                D QUE L34

     FILE 'DRUGU' ENTERED AT 12:43:29 ON 23 FEB 2007
                D QUE L42

     FILE 'WPIX' ENTERED AT 12:43:31 ON 23 FEB 2007
                D QUE L62
L83           28 SEA ABB=ON  L62 NOT L52

     FILE 'IPA' ENTERED AT 12:43:35 ON 23 FEB 2007
                D QUE L69

     FILE 'AGRICOLA, PASCAL, BIOTECHNO, ESBIOBASE, LIFESCI, DRUGB, BIOSIS,
     VETU, TOXCENTER, ANABSTR, SCISEARCH' ENTERED AT 12:43:36 ON 23 FEB 2007
                D QUE L80
L84            7 SEA ABB=ON  L80 NOT L77

     FILE 'MEDLINE' ENTERED AT 12:43:43 ON 23 FEB 2007
                D QUE L20
L85            2 SEA ABB=ON  L20 NOT L18

     FILE 'STNGUIDE' ENTERED AT 12:43:53 ON 23 FEB 2007

     FILE 'MEDLINE, CAPLUS, WPIX, BIOSIS, TOXCENTER, SCISEARCH' ENTERED AT
     12:44:24 ON 23 FEB 2007
L86           40 DUP REM L85 L82 L83 L84 (5 DUPLICATES REMOVED)
                     ANSWERS '1-2' FROM FILE MEDLINE
                     ANSWERS '3-10' FROM FILE CAPLUS
                     ANSWERS '11-35' FROM FILE WPIX
                     ANSWERS '36-39' FROM FILE TOXCENTER
                     ANSWER '40' FROM FILE SCISEARCH
                D IALL 1-2
                D IBIB ED ABS HITIND 3-10
                D IALL ABEQ TECH HIT HITSTR 11-35
                D IALL 36-40

     FILE 'HOME' ENTERED AT 12:45:49 ON 23 FEB 2007

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